

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07D 285/36, 513/04, 281/10, A61K 31/85	A1	(11) International Publication Number: WO 94/18184
(12) International Filing Date: 15 February 1993 (15.02.93)	GB	(13) International Publication Date: 18 August 1994 (18.08.94)
(30) Priority Data: 9303013-8 9315155-3	GB	(81) Designated States: AT, AU, BE, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BI, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TO).
(71) Applicant (for all designated States except US): THE WELL-FORMED FOUNDATION LIMITED (GB/CB); Unicorn House, 160 Euston Road, London NW1 2BP (GB).	GB	(72) Inventors and (73) Inventor/Applicant (for US only): BREADDY, Lawrence, Edward (US/US); 3924 Winthrop Drive, Raleigh, NC 27609 (US); HODGSON, Gordon, Lewis, Jr. (US/US); 20 Cobblestone Court, Durham, NC 27713 (US).
(74) Agent: CHAPMAN, Paul, William, The Wellcome Foundation Limited, Langley Court, Beckenham, Kent BR3 3BS (GB).	GB	(54) Title: HYPOLIPIDAEMIC COMPOUNDS

(57) Abstract	<p>The invention provides a compound of formula (I), wherein 1 is an integer of from 0 to 4; n is an integer of from 0 to 2; X is an aromatic or non-aromatic monocyclic or bicyclic ring system having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the diazepole ring) wherein optionally one or more of the carbon atoms is replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur; with the proviso that at least one of R, R¹, R² and R³ is hydroxy or a group containing hydroxy, and salts, solvates and physiologically functional derivatives thereof, pharmaceutical formulations comprising each compound, processes for their preparation and their use in reducing the acid uptake and hence as hypolipidaemic agents.</p> <div data-bbox="876 1428 1104 1680"> <p>(I)</p> </div>
---------------	--

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GR	Greece	MY	Malaysia
BE	Belgium	HR	Croatia	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BR	Brazil	IT	Italy	PL	Poland
BY	Belarus	JP	Japan	PT	Portugal
CA	Canada	KZ	Kazakhstan	RO	Romania
CF	Central African Republic	KG	Kyrgyzstan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Cote d'Ivoire	KZ	Kazakhstan	SI	Slovenia
CM	Cameroon	LA	Laos	SK	Slovakia
CN	China	LR	Liberia	SN	Senegal
CO	Colombia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TM	Turkmenistan
ES	Spain	MG	Madagascar	UA	Ukraine
FI	Finland	NL	Netherlands	UZ	Uzbekistan
FR	France	NP	Nepal	VN	Viet Nam
GA	Gabon				

HYPOLIPIDAEMIC COMPOUNDS

The present invention is concerned with new hypolipidaemic compounds, with processes and novel intermediates for their preparation, with pharmaceutical compositions containing them and with their use in medicine, particularly in the prophylaxis and treatment of hyperlipidaemic conditions, such as atherosclerosis.

Hypolipidaemic conditions are often associated with elevated plasma concentrations of low density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol. Such concentrations may be reduced by decreasing the absorption of bile acids from the intestine. One method by which this may be achieved is to inhibit the bile acid active uptake system in the terminal ileum. Such inhibition stimulates the conversion of cholesterol to bile acid by the liver and the resulting increase in demand for cholesterol produces a corresponding increase in the rate of clearance of LDL and VLDL cholesterol from the blood plasma or serum.

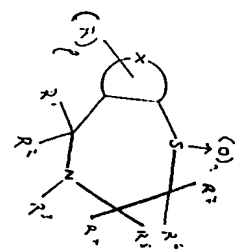
There has now been identified a novel class of heterocyclic compounds which reduce the plasma or serum concentrations of LDL and VLDL cholesterol and in consequence are particularly useful as hypolipidaemic agents. By decreasing the concentrations of cholesterol and cholesterol ester in the plasma, the compounds of the present invention retard the build-up of atherosclerotic lesions and reduce the incidence of coronary heart disease-related events. The latter are defined as cardiac events associated with increased concentrations of cholesterol and cholesterol ester in the plasma or serum.

For the purposes of this specification, a hyperlipidaemic condition is defined as any condition wherein the total cholesterol concentration (LDL + VLDL) in the plasma or serum is greater than 240mg/dL (6.21mmol/L) (J. Amer. Med. Assn. 256, 20, 2849-2858 (1986).

USP 3,362,962 describes a genus of benzothiazepines outside the scope of the present invention which have muscle-relaxant and anticonvulsant activity; there is no disclosure in the patent specification that the compounds described therein may be useful as hypolipidaemic agents.

According to the present invention, there is provided a compound of formula (I)

2



wherein

l is an integer of from 0 to 4;

n is an integer of from 0 to 2;

R is an atom or group selected from halogen, cyano, hydroxy, nitro, alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, alkyl, alkenyl, -O(CH₂)_pSO₂R¹¹, -O(CH₂)_pNR¹¹R¹², -O(CH₂)_pNR¹¹R¹²R¹⁴, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₂NR¹¹R¹² and -SO₂R¹¹ or R is a group -OCH₂O- which forms a further ring attached to X wherein p is an integer of from 1 to 4, R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl and R¹⁴ is hydrogen or C₁₋₆ alkyl, wherein said alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, alkyl and alkaryl groups are optionally substituted by one or more atoms or groups selected from halogen, hydroxy, nitro, nitrile, alkyl, alkoxy, -COR¹¹, -CO₂R¹¹, -SO₂R¹¹ wherein R¹¹ is as hereinbefore defined and -NR¹⁴R¹⁵ wherein R¹⁴ is as hereinbefore defined and R¹⁵ is hydrogen or C₁₋₆ alkyl;

R¹ is hydrogen or C₁₋₆ alkyl;

R² is an atom or group selected from hydrogen, C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₁₋₄ alkoxy, pyrryl, thienyl, pyridyl, 1,3-benzodioxolo, phenyl and naphthyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₂R¹¹ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), -O(CH₂)_pNR¹¹R¹², -O(CH₂)_pN⁺R¹¹R¹²R¹³ and -O(CH₂)_pSO₂R¹¹ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R³ is hydrogen, hydroxy C₁₋₆ alkyl, alkoxy or -O-C₁₋₆ Acyl;

R⁴ is a group independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, oxo, -OR¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁵, -SR¹⁴, -S(O)C₁₋₆ alkyl, -SO₂R¹⁴ and -SO₃R¹⁴ (wherein R¹⁴ and R¹⁵ are as hereinbefore defined);

R⁵ is a group independently selected from C₂₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, oxo, -OR¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁵, -SR¹⁴, -S(O)C₁₋₆ alkyl, -SO₂R¹⁴ and -SO₃R¹⁴ (wherein R¹⁴ and R¹⁵ are as hereinbefore defined);

or R⁴ and R⁵ together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which is optionally substituted by one or more atoms or groups independently selected from halogen, -CO₂R¹⁴, -SO₃R¹⁴ and -NR¹⁴R¹⁵ (wherein R¹⁴ and R¹⁵ are as hereinbefore defined);

R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆ alkyl; and

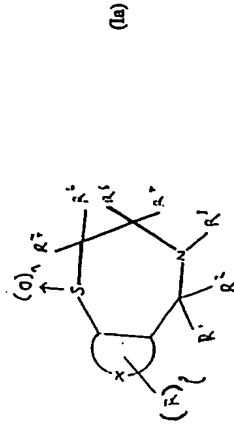
X is an aromatic or non-aromatic monocyclic or bicyclic ring system having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the thiazepine ring) wherein optionally one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur;

or X is an aromatic or non-aromatic monocyclic or bicyclic ring system having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the thiazepine ring) wherein one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur

with the proviso that at least one of R, R², R⁴ and R⁵ is hydroxy or a group containing hydroxy;

and salts, solvates and physiologically functional derivatives thereof.

Preferably the present invention provides a compound of formula (Ia):



wherein

l is an integer of from 0 to 4;

n is an integer of from 0 to 2;

R is an atom or group selected from halogen, cyano, hydroxy, nitro, alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, aralkyl, alkaryl, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹ and -SO₃R¹¹ wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl, wherein said alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, aralkyl and alkaryl groups are optionally substituted by one or more atoms or groups selected from halogen, hydroxy, nitro, nitrile, alkyl, alkoxy, -COR¹¹, -CO₂R¹¹, -SO₃R¹¹ wherein R¹¹ is as hereinbefore defined and -NR¹⁴R¹⁵ wherein R¹⁴ and R¹⁵ are as hereinbefore defined;

R¹ is hydrogen or C₁₋₆ alkyl;

R² is an atom or group selected from hydrogen, C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₁₋₄ alkoxy, pyrryl, thienyl, pyridyl, 1,3-benzodioxolo, phenyl and naphthyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₃R¹¹ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), -O(CH₂)_p NR¹¹R¹², -O(CH₂)_p N⁺R¹¹R¹²R¹³ and -O(CH₂)_p SO₃R¹¹ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R³ is selected from hydrogen, hydroxy and C₁₋₆ alkyl;

R⁴ is a group independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, -OR¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁵ and -SO₃R¹⁴ (wherein R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁₋₆ alkyl);

R⁵ is a group independently selected from C₂₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, -OR¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁵ and -SO₃R¹⁴ (wherein R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁₋₆ alkyl);

or R⁴ and R⁵, together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which is optionally substituted by one or more atoms or groups independently selected from halogen, -OR¹⁴, -CO₂R¹⁴, -SO₃R¹⁴ and -NR¹⁴R¹⁵ (where R¹⁴ and R¹⁵ are as hereinbefore defined);

R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆ alkyl; and

X is an aromatic or non-aromatic monocyclic or bicyclic ring system having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the thiadiazine ring) wherein optionally one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur.

with the proviso that at least one of R, R², R⁴ and R⁵ is hydroxy or a group containing hydroxy;

and salts, solvates and physiologically functional derivatives thereof.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent, i.e. basic, compounds. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulphuric and sulphuric acids, and organic acids, such as acetic, benzenesulphonic, benzoic, citric, ethanesulphonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulphonic, succinic, p-toluenesulphonic, tartaric and trifluoroacetic

acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

Salts having a non-pharmaceutically acceptable anion are within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in non-therapeutic, for example, *in vitro*, applications.

The term "physiologically functional derivative" as used herein refers to any physiologically acceptable derivative of a compound of the present invention, for example, as ester, which upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) such a compound or an active metabolite thereof.

A further aspect of the present invention is products of the compounds of the invention. Such products can be metabolised *in vivo* to give a compound according to the invention. These products may or may not be active in their own right.

The compounds of the present invention can also exist in different polymorphic forms, for example, amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds of the present invention are within the scope of the invention and are a further aspect thereof.

The term "alkyl" as used herein refers, unless otherwise stated, to a monovalent straight or branched chain radical. Likewise, the term "alkoxy" refers to a monovalent straight or branched chain radical attached to the parent molecular moiety through an oxygen atom. The term "aryl" refers to an aromatic monocyclic or bicyclic ring system comprising from 6 to 10 carbon atoms and optionally substituted by one or more atoms or groups selected from halogen, hydroxy, nitro, nitrile, alkoxy, -COR¹¹, -CO₂R¹¹, -SO₃R¹¹ wherein R¹¹ is as hereinbefore defined and -NR¹⁴R¹⁵ wherein R¹⁴ and R¹⁵ are as hereinbefore defined. The term "heteroaryl" refers to an aromatic monocyclic or bicyclic ring system comprising from 5 to 10 carbon atoms wherein one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur, which ring system is optionally substituted by one or more atoms or groups selected from halogen, hydroxy, nitro, nitrile, alkoxy, -COR¹¹, -CO₂R¹¹, -SO₃R¹¹ wherein R¹¹ is as hereinbefore defined and -NR¹⁴R¹⁵ wherein R¹⁴ and R¹⁵ are as hereinbefore defined. The term "aryloxy" refers to an aryl group as herein defined attached to the parent molecular moiety through an oxygen atom. The term "aryloxy" refers to an aryl group as herein defined

attached to a divalent C₁₋₆ alkylene group which is itself attached to the parent molecular moiety through an oxygen atom. The term "aralkyl" refers to an aryl group as herein defined attached to a divalent C₁₋₆ alkylene group which is itself attached to the parent molecular moiety. The term "alkaryl" refers to an alkyl group as herein defined attached to an aryl group as herein defined which is itself attached to the parent molecular moiety. The term "halogen" refers to Fluorine, Chlorine, Bromine and Iodine.

The compounds of formula (I) can exist in forms wherein one or more of the carbon centres -C(R⁶)(R⁷), -C(R⁴)(R⁵), and -C(R¹)(R²) is/are chiral. The present invention includes within its scope each possible optical isomer substantially free, i.e. associated with less than 5%, of any other optical isomer(s), and mixtures of one or more optical isomers in any proportions, including racemic mixtures.

For the purposes of this specification, the absolute chiralities of -C(R⁴)(R⁵) and -C(R¹)(R²) are given in the order -C(R⁴)(R⁵), then -C(R¹)(R²). For example, the prefix "(RS)" denotes an (R)-configuration at -C(R⁴)(R⁵) and an (S)-configuration at -C(R¹)(R²) and the prefix "(RS,SR)" denotes a mixture of two isomers wherein one is (R)- at -C(R⁴)(R⁵) and (S)- at -C(R¹)(R²) and the other is (S)- at -C(R⁴)(R⁵) and (R)- at -C(R¹)(R²). Other permutations will be clear to the skilled person.

In those cases where the absolute stereochemistry at -C(R⁴)(R⁵) and -C(R¹)(R²) has not been determined, the compounds of the invention are defined in terms of the relative positions of the R⁴/R⁵ and R¹/R² substituents. Thus those compounds wherein the bulkier of the R⁴ and R⁵ substituents, i.e. the substituent of higher mass, and the bulkier of the R¹ and R² substituents are both located on the same side of the thiazepine ring are referred to herein as "cis", and those compounds wherein the two bulkier substituents are located on opposite sides of the ring are referred to as "trans". It will be evident to a skilled person that both "cis" and "trans" compounds of the invention can each exist in two enantiomeric forms which are individually designated "(+)" or "(-)" according to the direction of rotation of a plane of polarised light when passed through a sample of the compound. Cis or trans compounds of the invention in which the individual enantiomers have not been resolved are referred to herein using the prefix "(+-)".

Preferred compounds of formula (I) having particularly desirable hypolipidaemic properties include those wherein

1 is 0, 1, or 2;

n is 1 or 2; and

R¹, R⁶ and R⁷ are all hydrogen;

R³ is hydrogen or OH.

Of these, the trans isomers of those compounds wherein

(i) 1 is 0 or 1;

n is 2; and

R⁴ and R⁵ are groups independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, wherein said alkyl, alkenyl, or alkynyl group may be substituted by one or more hydroxy groups, or R⁴ and R⁵, together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which can be substituted by one or more hydroxy groups;

(ii) 1 is 0 or 1;

n is 2;

R² is a phenyl group which may be substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₃R¹¹ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), -O(CH₂)_pNR¹¹R¹², -O(CH₂)_pNR¹¹R¹²R¹³ and -O(CH₂)_pSO₃R¹¹ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R⁴ and R⁵ are groups independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, wherein said alkyl, alkenyl, or alkynyl group may be substituted by one or more hydroxy groups, or R⁴ and R⁵, together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which can be substituted by one or more hydroxy groups; and

(iii) 1 is 0 or 1;

n is 2;

R² is a phenyl group which may be substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₃R¹¹ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), -O(CH₂)_pNR¹¹R¹², -O(CH₂)_pNR¹²R¹³ and -O(CH₂)_pSO₃R¹¹ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R⁴ and R⁵ are groups independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups can be substituted by one or more hydroxy groups; and

X is a fused phenyl, naphthyl, pyrrolyl, thieryl, or pyridyl group; are particularly preferred.

Compounds of formula (I) having exceptional hypolipidaemic properties include:-

- (+)-trans-3-ethyl-2,3,4,5-tetrahydro-3-((2R)-2-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-3-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-7-methoxy-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide 0.5 hydrate;

- (+)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride;
- (+)-cis-3-ethyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride;
- (+)-trans-3-ethyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4-trifluoro-(2S)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4-trifluoro-(2S)-2-butanol S,S-dioxide;
- (+)-trans-3-Ethyl-2,3,4,5-tetrahydro-3-(3-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-3-Ethyl-2,3,4,5-tetrahydro-3-(2(R)-2-hydroxybutyl)-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-1-(3-Ethyl)-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl)-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2(S)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl)-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2(S)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl)-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2(S)-2-butanol S,S-dioxide;
- (+)-trans-3-((3-ethyl-2,3,4,5-tetrahydro-5-phenyl)-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-8-yl)oxy)propane-sulfonic acid 1,1-dioxide;
- (+)-trans-3-((3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl)-1,4-benzothiazepin-8-yl)oxy)ethyltrimethylammonium iodide 1,1-dioxide;
- (+)-trans-1-(3-Ethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2-butanol S,S-dioxide;
- (+)-trans-3-((3-ethyl-2,3,4,5-tetrahydro-5-phenyl)-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-8-yl)oxy)ethyltrimethylammonium iodide 1,1-dioxide;

- (+)-trans-3-(3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl)-1,4-benzothiazepin-8-yloxy)propanesulfonic acid 1,1-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dithoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
 (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-1-butanol S,S-dioxide;
 (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-1-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2-butanone S,S-dioxide;

Of the above the following compounds are most preferred:-

- (+)-trans-1-(3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-7-methoxy-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-(2S)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-(2S)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(S)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;

According to further aspects of the invention, there are also provided:

- (a) compounds of formula (I) and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof for use as therapeutic agents, particularly in the prophylaxis and treatment of clinical conditions for which a bile

acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition such as atherosclerosis;

- (b) pharmaceutical compositions comprising a compound of formula (I) and/or one of its pharmaceutically acceptable salts, solvates, or physiologically functional derivatives, at least one pharmaceutically acceptable carrier and, optionally, one or more other physiologically active agents;
- (c) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis;
- (d) a method of inhibiting the absorption of bile acids from the intestine of a mammal, such as a human, which comprises administering an effective bile acid absorption inhibiting amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (e) a method of reducing the blood plasma or serum concentrations of LDL and VLDL cholesterol in a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (f) a method of reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol and cholesterol ester reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (g) a method of increasing the faecal excretion of bile acids in a mammal, such as a human, which comprises administering an effective bile acid faecal excretion increasing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;

- (h) a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a bile acid uptake inhibitor is indicated, for example, a hyperlipidaemic condition, such as atherosclerosis, which comprises administering a therapeutically effective amount of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal;
- (i) a method of reducing the incidence of coronary heart disease-related events in a mammal, such as a human, which comprises administering an effective coronary heart disease-related events reducing amount of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof;
- (j) a method of reducing the concentration of cholesterol in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I);
- (k) processes for the preparation of compounds of formula (I) (including salts, solvates and physiologically functional derivatives thereof as defined herein); and
- (l) compounds of formula (II) for use as intermediates in the preparation of compounds of formula (I).

Hereinafter all references to "compound(s) of formula (I)" refer to compound(s) of formula (I) as described above together with their salts, solvates and physiologically functional derivatives as defined herein.

The amount of a compound of formula (I) which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode of administration and the clinical condition of the recipient. In general, a daily dose is in the range of from 0.0001mg to 100mg, typically from 0.0001 to 5 mg, per day per kilogram bodyweight, for example 0.005-0.5mg/kg/day, preferably 0.001 to 0.5mg/kg/day. An intravenous dose can, for example, be in the range of from 0.001mg to 0.5 mg/kg, which can conveniently be administered as an infusion of from 0.03mg to 50mg per kilogram per minute. Infusion fluids suitable for this purpose can contain, for example, from 0.0003mg to 5mg, typically from 0.003mg to 5mg, per millilitre. Unit doses can contain, for example, from 0.01mg to 10mg of the active

compound, preferably from 0.1 to 5mg. Thus ampoules for injection can contain, for example, from 0.01mg to 100mg and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.01mg to 1000mg, typically from 0.01mg to 60mg, preferably 0.1 mg to 10mg. In the case of pharmaceutically acceptable salts, the weights indicated above refer to the weight of the benzothiazepine ion derived from the salt.

For the prophylaxis or treatment of the conditions referred to above, the compounds of formula (I) can be used as the compound *per se*, but are preferably presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances can also be present including other compounds of formula (I). The pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

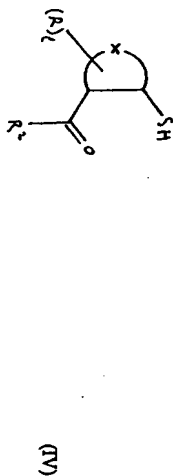
Pharmaceutical compositions according to the present invention include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound of formula (I) which is being used. Enteric-coated and enteric-coated controlled release formulations are also within the scope of the invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I), as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can

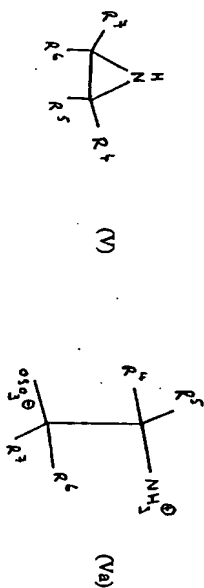
17

wherein $1, R, R^2, R^4$ to R^7 and X are as hereinbefore defined, by, for example, azeotropic distillation or refluxing in the presence of a suitable drying agent, such as molecular sieves, in a suitable solvent, for example, 2,6-lutidine, in the presence of an acid, such as HCl.

Compounds of formula (III) can be prepared by reacting a compound of formula (IV)

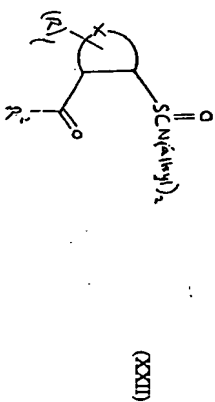


wherein $1, R, R^2$ and X are as hereinbefore defined, with a compound of formula (V), or preferably with a compound of formula (Va)



wherein R^4 to R^7 are as hereinbefore defined, typically in a polar solvent, for example, methanol.

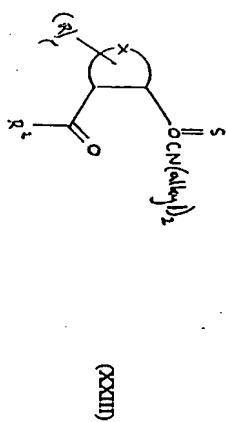
Compounds of formula (IV) can be prepared by hydrolysis of a compound of formula (XXII)



18

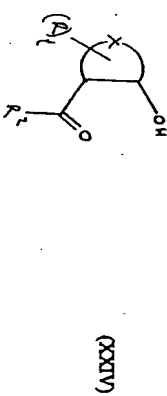
wherein $1, X, R$ and R^2 are as hereinbefore defined with, for example, a base, such as KOH in a suitable solvent such as methanol/THF.

Compounds of formula (XXII) can be prepared by heating a compound of formula (XXIII)



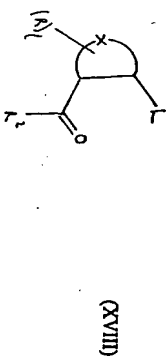
wherein $1, X, R$ and R^2 are as hereinbefore defined in a non-polar solvent such as (Ph)₂O.

Compounds of formula (XXIII) can be prepared by reaction of a compound of formula (XXIV)



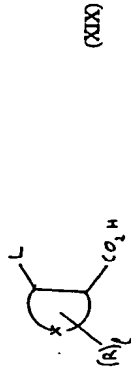
wherein $1, X, R$ and R^2 are as hereinbefore defined with halo-CSN(alkyl)₂, for example, ClCSNMe₂ in a suitable solvent such as DMAP/Et₃N.

Compounds of formula (III) can also be prepared by reacting a compound of formula (XVIII)



wherein L, R, R² and X are as hereinbefore defined and L is a suitable leaving group, for example, halogen, with a compound of formula HSC(R⁶)(R⁷)(R⁸)(R⁹)NH₂ wherein R⁴ to R⁷ are as hereinbefore defined.

Compounds of formula (XVIII) can be prepared by reacting a compound of formula (XX)



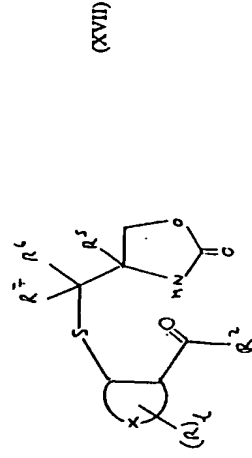
wherein L, R, R² and X are as hereinbefore defined, with a compound of formula R²H wherein R² is as hereinbefore defined, typically by a Friedel-Crafts reaction using, for example, aluminium chloride.

Alternatively, compounds of formula (XVIII) can be prepared by reacting a compound of formula (XVIIIa)



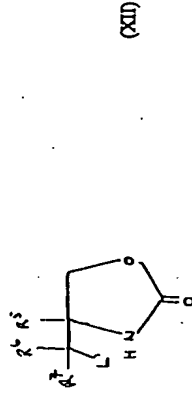
wherein L, R, R² and X are as hereinbefore defined with a suitable acid halide, e.g. R²COCl wherein R² is as hereinbefore defined, by a Friedel-Crafts reaction using, for example, aluminium chloride.

Compounds of formula (III) wherein R⁴ is -CH₂OH can also be prepared by hydrolysis, preferably with base, of a compound of formula (XVII)



wherein L, R, R², R⁵ to R⁷ and X are as hereinbefore defined, using, for example, KOH in aq. ethanol.

Compounds of formula (XVII) can be prepared by reacting a compound of formula (IV) wherein m, R, R² and X are as hereinbefore defined, with a compound of formula (XII)



wherein R⁵ to R⁷ are as hereinbefore defined and L' is a suitable leaving group, for example, -OTosyl, typically in a polar aprotic solvent, such as DMF, in the presence of a base, for example, NaH.

Compounds of formula (IV) can be prepared by reacting a compound of formula (VI)

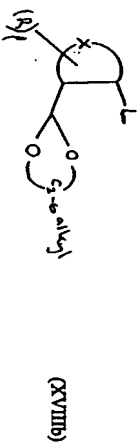


21

wherein L, R and X are as hereinbefore defined, with a compound of formula R^2CN wherein R^2 is as hereinbefore defined. The reaction is typically carried out by metalation of compound (VI) using, for example, *n*-butyl lithium in the presence of N,N,N',N' -tetramethylethylenediamine (TMEDA) followed by reaction with the appropriate nitrile in a non-polar solvent, for example, cyclohexane.

Compounds of formula (IV) can also be prepared by reacting a compound of formula (XVIII) as hereinbefore defined with sodium sulphide ($NaSH$) on metalation when L is halogen followed by reaction with sulphur.

Alternatively, compounds of formula (IV) can be prepared from a compound of formula (XVIIIb)



wherein L, R , R^2 , X and L are as hereinbefore defined and preferably C_{2-6} alkyl is $-CH_2-CH_2-$ or $-CH_2-C(Me)_2-CH_2-$, by metalation of a compound of formula (XVIIIa) using, for example, magnesium or *n*-butyllithium followed by reaction with sulphur (S₈) and hydrolysis of the alkylendioxy protecting group with, for example, acid.

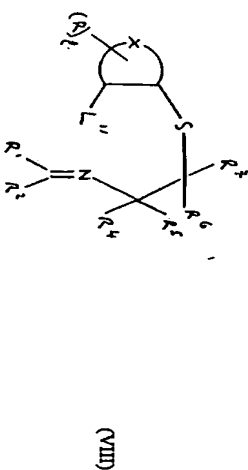
Compounds of formula (XVIIIb) can be prepared from the corresponding compounds of formula (XVIIIa) by reaction with the appropriate C_{2-6} diol, preferably 1, 2-ethanediol or 2,2-dimethyl-1,3-propanediol in a suitable solvent, for example toluene and preferably in the presence of a catalyst such as *p*-toluenesulfonic acid.

Compounds of formulae (V), (Va), (XIX), (XII), (VI) and R^2CN as hereinbefore defined can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature. Thus compounds of formula (V) can be prepared from the corresponding 2-substituted 2-aminoethanols or from compounds of formula (Va) and compounds of formula (XII) from the corresponding 2-substituted-2-amino-1,3-propanediols. 2-substituted-2-aminoethanols and 2-substituted-2-amino-1,3-propanediols can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature.

22

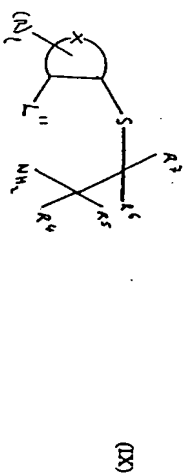
Compounds of formula (I) wherein $n = 0$ and R^1 is not hydrogen can be obtained by reacting the corresponding compound of formula (II) with, for example, an organometallic compound, such as R^1Li , R^1Cu , R^1Zn , or R^1MgBr wherein R^1 is as hereinbefore defined other than hydrogen.

Compounds of formula (I) wherein $n = 0$ and R^3 is hydrogen can also be prepared by cyclising a compound of formula (VIII)



wherein L, R , R^1 , R^2 , R^4 to R^7 and X are as hereinbefore defined and L'' is halogen, for example, bromine, by treatment with strong base, for example, *n*-butyllithium, in a suitable solvent, such as THF, at a low temperature, for example, $-78^\circ C$.

Compounds of formula (VIII) can be prepared by reaction of a compound of formula (IX)



wherein L, L'' , R , R^4 to R^7 and X are as hereinbefore defined, with a compound of formula $R^1R^2C=O$ wherein R^1 and R^2 are as hereinbefore defined. The reaction is typically carried

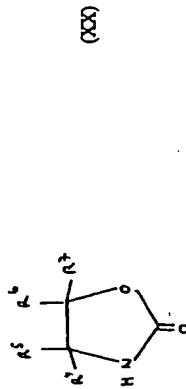
out in a non-polar solvent, for example, toluene, in the presence of an acid, such as p-toluenesulphonic acid.

Compounds of formula (IX) can be prepared by reacting a compound of formula (XI).



wherein L, L', R and X are as hereinbefore defined, with a compound of formula (V) wherein R⁴ to R⁷ are as hereinbefore defined, typically in a polar solvent, such as methanol.

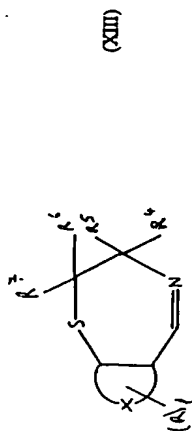
Compounds of formula (IX) can also be prepared by reacting a compound of formula (XX) as hereinbefore defined with a compound of formula (XXX).



wherein R⁴ to R⁷ are as hereinbefore defined, in the presence of a Lewis acid, for example, lithium chloride, at an elevated temperature, such as 170-210 °C.

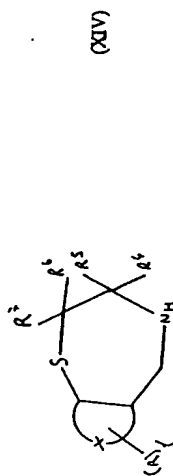
Compounds of formulae R¹R²C=O as hereinbefore defined, (XI) and (XX) can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature. Thus compounds of formula (XI) can be prepared from the corresponding disulphides and compounds of formula (XX) from the corresponding 2-substituted 2-aminoethanols.

Compounds of formula (I) wherein n = 0 and R¹ and R³ are both hydrogen can also be obtained by reacting a compound of formula (XIII).



wherein L, R, R⁴ to R⁷ and X are as hereinbefore defined, with, for example, an organometallic compound, such as R²Li, R²Cu, R²Zn, or R²MgBr wherein R² is as hereinbefore defined.

Compounds of formula (XIII) can be prepared by dehydrogenating the corresponding compound of formula (XIV).

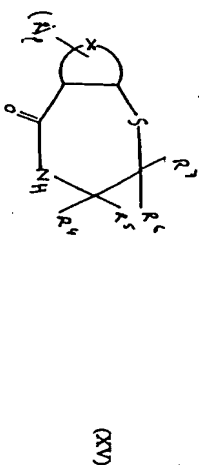


wherein L, R, R⁴ to R⁷ and X are as hereinbefore defined, using, for example, an oxidising agent, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in a suitable solvent, such as toluene, or preferably KMnO₄ in a suitable solvent, such as t-butanol/H₂O.

Alternatively, compounds of formula (XIII) can be prepared by reacting a compound of formula (IV) wherein R² is hydrogen with a compound of formula (V) or (Va).

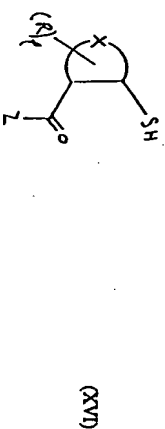
25

Compounds of formula (XIV) can be prepared by reducing the amide carbonyl group of the corresponding compound of formula (XV)



wherein $1, R, R^4$ to R^7 and X are as hereinbefore defined, using, for example, lithium aluminium hydride.

Compounds of formula (XV) can be prepared by reacting a compound of formula (XXV)

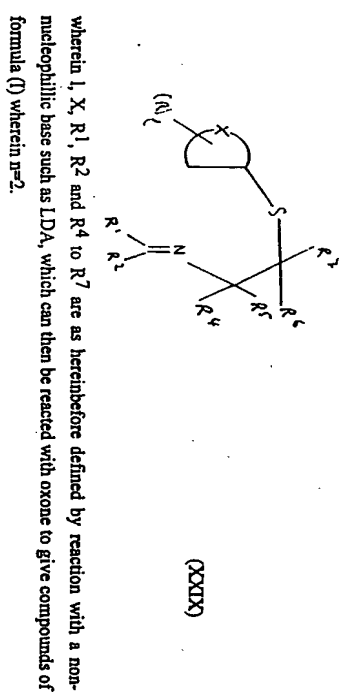


wherein $1, R$ and X are as hereinbefore defined and Z is C_{1-4} alkoxy, for example, methoxy, with a compound of formula (V) or (Va) wherein R^4 to R^7 are as hereinbefore defined.

The compound of formula (XVI) wherein X is benzo can be prepared from a suitably (R_1), substituted 2,2-dithiosuccinic acid or when $1=0$, from commercially available 2,2'-dithiosuccinic acid by methods known to those skilled in the art. Compounds of formula (XVI) wherein 1 is not 0 can be obtained commercially or prepared by methods known to those skilled in the art or obtainable from the chemical literature.

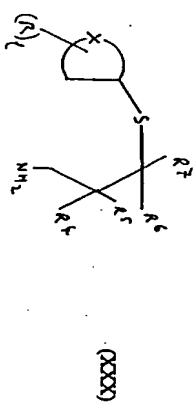
Alternatively compounds of formula (I) wherein $n=0$ and R^3 is hydrogen can be prepared by cyclising a compound of formula (XXIX)

26



wherein $1, X, R^1, R^2$ and R^4 to R^7 are as hereinbefore defined by reaction with a non-nucleophilic base such as LDA, which can then be reacted with oxone to give compounds of formula (I) wherein $n=2$.

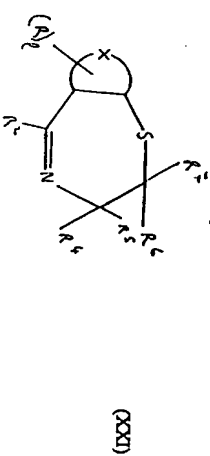
Compounds of formula (XXXIX) can be prepared from compounds of formula (XXX)



wherein $1, X$, and R^4 to R^7 are as hereinbefore defined, by reaction with R^2CHO wherein R^2 is as hereinbefore defined.

Compounds of formula (XXXIX) can be prepared by reaction of compound of formula (V) with compounds of formula (VI).

Compounds of formula (I) can also be prepared starting from compounds of formula (XXI).



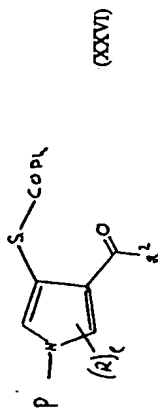
wherein $X, 1, R, R^2$ and R^5 to R^7 are as hereinbefore defined, by steps well known in the art.

Compounds of formula (XXI) can be prepared by following methods described herein which methods will be obvious to one skilled in the art.

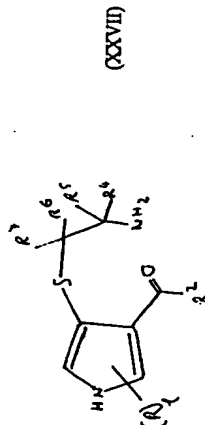
Compounds of formula (XXI) can also be prepared by reaction of compounds of formula (II) wherein $R^4 = CH_2OH$ by oxidation of the alcohol with, for example, SO_3 pyridine in $Et_3N/DMSO$.

Compounds of formula (I) wherein $R^3 = OH$, C_{1-6} alkoxy or $-OC_{1-6}$ acyl can be prepared from compounds of formula (I) wherein R^3 is hydrogen by oxidation of the nitrogen with, for example, oxone® (potassium peroxymonosulphate) in methanol/water optionally followed by reactions known in the art.

Compounds of formula (I) wherein X=pyrrolo can be prepared from compounds of formula (XXVI)



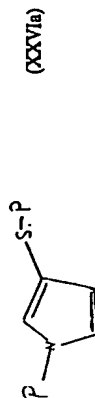
wherein P is a protecting group such as tri-isopropylsilyl, R_1 and R_2 are as hereinbefore defined by refluxing with a base such as NaOH followed by reaction with a compound of formula (V) or (Va) in a suitable solvent such as methanol. The resulting compound (XXVII)



wherein R_1 , R_2 , R^4 , R^5 , R^6 , and R^7 are as hereinbefore defined, is then reacted with for example lutidine/TSOH to give a compound of formula (II) wherein X=pyrrolo. These compounds can then be converted into compounds of formula (I) as previously described or

by reaction with 1) BH_3/THF and 2) N-methyl morpholine-N-oxide, $O_3O_4/tBuOH/THF$ at room temperature.

Compounds of formula (XXVI) can be prepared from compounds of formula (XXVIIa)



wherein P is as defined hereinbefore and can be the same or different, by reacting a compound of formula (XXVIIa) with a suitable acid halide compound, such as R^2COCl , wherein R^2 is as hereinbefore defined, by a Friedel-Crafts reaction using, for example, aluminium chloride.

The compound of formula (XXVIIa) can be prepared by first reacting pyrrolo with a strong base, for example n-butyllithium in an aprotic solvent such as THF, followed by N-protection with, for example TIPS-Cl (tri-isopropylsilyl chloride). The resulting N-protected pyrrolo is halogenated with, for example N-Bromosuccinimide (NBS), followed by metalation with, for example t-butyllithium and reaction with sulphur (S_8). The resulting sulphur compound is further s-protected with, for example TIPS-Cl.

Compounds formula (I) wherein X=pyridyl can be prepared from compounds of formula (XXVIII) wherein X=pyridyl by reaction with, for example, NaSH/DMSO and a compound of formula (V) or (Va).

The resulting compound of formula (III) wherein X is pyridyl, R_1 , R^2 , and R^4 to R^7 are as hereinbefore defined can be converted to a compound of formula (II) wherein X=pyridyl as previously described. These compounds of formula (II) can then be converted to compounds of formula (I) as previously described herein.

Side-chain manipulation: Compounds of formula (I) wherein R^4 is, for example, $-CH_2CH=CHCH_3$, can be hydrochlorinated using, for example, gaseous hydrogen chloride, to give the corresponding compound of formula (I) wherein R^4 is $-CH_2CHClCH_2CH_3$ and then hydrolysed using, for example, basic H_2O_2 , to give the corresponding compound of formula (I) wherein R^4 is $-CH_2CH(OH)CH_2CH_3$. Compounds of formula (I) wherein R^4 is $-CH_2CH(OH)CH_2CH_3$ can also be prepared by reducing and hydroxylating a compound of

formula (II) wherein R⁴ is -CH₂CH=CHCH₃ using, for example, diborane followed by acidification and subsequent oxidation with basic H₂O₂. Compounds of formula (III) wherein R⁴ is -CH₂OH can be cyclised as described earlier to give the corresponding compound of formula (II) wherein R⁴ is, for example -CHO₂H. The latter can be oxidised using, for example, SO₃/pyridine and Et₃N in DMSO, to give the corresponding compound of formula (II) wherein R⁴ is -CHO, alkylated using, for example, Ph₃P=CHCOCH₃ in toluene, to give the corresponding compound of formula (II) wherein R⁴ is, for example -CH=CHCOCH₃ and then (i) reduced using, for example, sodium borohydride in ethanol, to give the corresponding compound of formula (II) wherein R⁴ is -CH=CHCH(OH)CH₃ followed by reduction of the alkene, for example when n is 1 or 2 by catalytic hydrogenation using, for example, 10% Pd/C, to give the corresponding compound of formula (I) wherein R⁴ is -CH₂CH₂CH(OH)CH₃ or (ii) reduction of the alkene, for example when n is 1 or 2 by catalytic hydrogenation to give the corresponding compound of formula (I) wherein R⁴ is -CH₂CH₂COCH₃ followed by reduction of the ketone to give the corresponding compound of formula (I) wherein R⁴ is -CH₂CH₂CH(OH)CH₃. Alternatively, the compound of formula (II) wherein R⁴ is -CHO can be alkylated using a Wittig reagent, for example, Ph₃P⁺(CH₂)₁₋₅OH Br⁻ and n-BuLi, to give the corresponding compound of formula (II) wherein R⁴ is -CH=CH(CH₂)₀₋₄OH followed by reduction of the alkene, for example when n is 1 or 2 by catalytic hydrogenation to give the corresponding compound of formula (I) wherein R⁴ is -(CH₂)₂₋₆OH using, for example, 10% Pd/C.

The compound of formula (II) wherein R⁴ is -CHO can be alkylated using a Wittig reagent, for example, Ph₃P⁺=CHCH₂CF₃Br⁻ followed by conversion of the alkene as described hereinbefore.

Compounds of formula (I) wherein R² is hydroxyphenyl can be prepared by debenzoylation of the corresponding compound of formula (I) wherein R² is benzoyloxyphenyl using, for example, 30% aq. H₂O₂ in trifluoroacetic acid or 10% Pd/C/hydrogen.

Compounds of formula (I) wherein n = 0 and R³ is not hydrogen can be prepared by N-alkylation of the corresponding compound of formula (II) with an alkyl halide, such as methyl iodide, in a polar solvent, for example, acetonitrile, prior to reduction to the compound of formula (I).

Compounds of formula (I) wherein n = 1 or 2 can be prepared by oxidation of the corresponding compound of formula (I) wherein n = 0 or by oxidation of the corresponding compound of formula (III) wherein n = 0 prior to cyclisation and reduction to the compound

of formula (I) using suitable oxidation conditions, for example, in the case where n is to be 2, 30% aq. H₂O₂ in the presence of trifluoroacetic acid.

Individual optical isomers of compounds of formula (I) substantially free, of other optical isomers can be obtained either by chiral synthesis, for example, by the use of the appropriate chiral starting material(s), such as the aziridine (V), or by resolution of the products obtained from achiral syntheses, for example, by chiral hplc.

Optional conversion of a compound of formula (I) to a corresponding acid addition salt can be effected by reaction with a solution of the appropriate acid, for example, one of those recited earlier. Optional conversion to a corresponding base salt may be effected by reaction with a solution of the appropriate base, for example, sodium hydroxide. Optional conversion to a physiologically functional derivative, such as an ester, can be carried out by methods known to those skilled in the art or obtainable from the chemical literature.

For a better understanding of the invention, the following Examples are given by way of illustration and are not to be construed in any way as limiting the scope of the invention.

Synthetic Example 1

Preparation of (+)-trans-3-ethyl-2,3,4,5-tetrahydro-3-(2(R)-2-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide

(a) Ethyl 2-aminobutyrate hydrochloride

A slurry of 2-aminobutyric acid (100g, Aldrich) in absolute ethanol (300ml) was stirred under nitrogen at 0 °C and thionyl chloride (120.8g) was added dropwise. The reaction was stirred overnight at 0 °C and then gradually warmed to room temperature. The resulting white slurry was heated under reflux for 3 hours, left to cool for 10 minutes, then poured into chilled diethyl ether (600ml), with hand stirring. The suspension was filtered and the solid product dried to give the desired product (150g) as a white solid. ¹H NMR consistent with proposed structure.

(b) Ethyl 2-benzylideneminoaminobutyrate

A solution of the product from step (a) (149.6g), magnesium sulphate (74.3g), and triethylamine (246ml) in dichloromethane (1500ml) was stirred at room temperature under nitrogen and benzaldehyde (94.9g, Aldrich) was added dropwise. The mixture was stirred at room temperature for 3 hours then filtered. The filtrate was concentrated, triturated in diethyl ether, filtered and concentrated to yield the desired product as a yellow oil (174g). ¹H NMR consistent with the proposed structure.

(c) (±)-2-Ethyl-2-benzylidenamino-2-ethylhex-4-enoate

A solution of the product from step (b) (159g) in THF (100ml) was added to a suspension of potassium hydride (64g) in THF (350ml) at a temperature of about 0 °C. When addition was complete, the mixture was stirred at about 0 °C for 2 hours, then cooled using a dry ice/acetone bath and a solution of crotyl bromide (100g) in THF (50ml) added. When addition was complete, the mixture was stirred at room temperature for two days, then quenched with ethanol (60ml) to destroy excess hydride followed by pet. ether (1500ml) and water (25ml). The mixture was filtered and the filtrate evaporated in *vacuo* to give the desired product as a dark red oil. ¹H NMR consistent with the proposed structure.

(d) (±)-2-Ethyl-2-amino-2-ethylhex-4-enoate

4N Aqueous HCl (170ml) was added to a solution of the product from step (c) in pet. ether (1500ml). When addition was complete, the mixture was stirred for 2 hours at about 0 °C. The aqueous phase was separated, washed with pet. ether and poured into 2M Na₂CO₃ (200ml) at about 0 °C. The pH was adjusted to 9 by the addition of further Na₂CO₃ and the mixture extracted with ether. The combined extracts were dried and evaporated in *vacuo* to give the desired product as an oil. ¹H NMR consistent with the proposed structure.

(e) (±)-2-Amino-2-ethylhex-4-en-1-ol

A solution of the product from step (d) (116.7g) in THF (100ml) was added to a 1M solution of lithium aluminium hydride in THF (800ml) at about 0 °C. When addition was complete, the mixture was stirred overnight at room temperature, then 50% w/v aq. NaOH (200ml) was added. The organic phase was separated, washed with brine, dried and evaporated in *vacuo*. The residue was distilled to give the desired product as an oil (29.3g). ¹H NMR consistent with the proposed structure.

(f) (±)-2-But-2-enyl-2-ethylaziridine

Chlorosulphonic acid (18ml) was added to a solution of the product from step (e) (32.3g) in acetonitrile (100ml) at about 0 °C. When addition was complete, the mixture was warmed to room temperature. The resulting crystals were filtered off, washed with acetonitrile/pet. ether, dried, taken up in a mixture of 50% w/v aq. KOH (100ml) and water (55ml) and distilled over KOH to give the desired product as a colourless oil (16.1g). ¹H NMR consistent with the proposed structure.

(g) 2-Thiobenzophenone

A solution of N,N,N',N'-tetramethylethylenediamine (TMEDA) (104.6g) in cyclohexane (500ml) was cooled and 2.5M n-butyllithium (366ml) was added. A solution of thiophenol (50.0g) in cyclohexane (100ml) was added slowly to the butyllithium solution and the reaction was stirred at room temperature overnight. Benzonitrile (46.4g, Aldrich) in cyclohexane (100ml) was added to give a slurry which was stirred overnight at room temperature. Water (500ml) was added and the mixture stirred for 30 minutes, then the aqueous layer was separated and treated with solid sodium hydroxide to give pH 14. The solution was boiled for 90 minutes, cooled to room temperature and acidified to pH 1-2 with conc. HCl. The acidic solution was extracted with dichloromethane and the combined extracts dried, then concentrated to give a red oil. The oil was treated with 1N NaOH, extracted with dichloromethane and the aqueous layer separated and treated with conc. HCl to give an oil. The oil was extracted into dichloromethane and the combined extracts dried, then concentrated to give the desired product as an orange-red oil (83.4g). ¹H NMR consistent with proposed structure.

(h) (±)-2-Ethyl-3-but-2-enyl-5-phenyl-2,3-dihydrobenzobiazepine

The products from steps (f) (8.0g) and (g) (12.9g) were taken up in 2,6-lutidine, stirred for 2 hours and conc. HCl (5ml) was added. When addition was complete, the mixture was azeotroped overnight at 180 °C, then cooled and evaporated in *vacuo*. The residue was taken up in 5% w/v aq. NaHCO₃ and the solution extracted with ethyl acetate. The combined extracts were washed with brine, dried and evaporated in *vacuo*. The residue was flash chromatographed on silica gel using 80:20 hexane/ethyl acetate as eluant to give the desired product as an orange oil (18.4g). ¹H NMR consistent with the proposed structure.

(i) (+)-3-(2R)-2-Hydroxybutyl-3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine

A 1M solution of diborane in THF (31.7mL) was added to a solution of the product from step (h) in THF (150mL). When addition was complete, the mixture was stirred overnight at room temperature, then 50% w/v aq. HCl (100mL) was added. When addition was complete, the mixture was concentrated in *vacuo* to remove the THF. 50% w/v aq. NaOH and ethyl acetate were added to the remaining aqueous phase and the organic phase separated, dried and evaporated in *vacuo*. The residue

was taken up in THF (150mL) and 3N NaOH(32mL) followed by 30% H₂O₂(17.7g) were added. When addition was complete, the mixture was stirred at room temperature for 3.5 hours, then satd. aq. Na₂CO₃ was added. The organic phase was separated, dried and evaporated in *vacuo*. The residue was chromatographed on silica gel using 70:30 hexane/ethyl acetate as eluant to give the desired product as an oil (1.5g).

(i) (+)-Trans-3-ethyl-2,3,4,5-tetrahydro-3-(2R)-2-hydroxybutyl-5-phenyl-1,4-benzothiazepine 1,1-dioxide

A solution of the product from step (i) (1.5g) in trifluoroacetic acid (25mL) was added to a solution of 30% H₂O₂(1.4g) in trifluoroacetic acid (5mL). When addition was complete, the mixture was stirred overnight at room temperature, then added to deionized water(300mL), basified with 1N NaOH and stirred for 1 hour. The resulting precipitate was filtered off and triturated with 1N NaOH for 1 hour, then filtered and dried to give the desired product as a white solid, mp 149-151 °C (1.5g).

Analysis: Calcd. C 66.24; H 7.36; N 3.68; S 8.40

Found: C 66.31; H 7.25; N 3.64; S 8.49

¹H NMR (DMSO-d₆): δ: 0.77-0.93 (6H, m, 2x CH₃), 1.21-1.38 (2H, m, CH₂), 1.69-1.85 (3H, m, CH₂ + NH), 2.30-2.43 (1H, m, CH), 3.59-3.69 (1H, m, OH), 3.62(2H, q, CH₂SO₂), 6.26 (1H, s, CHPh), 6.57-6.63 (1H, m, ArH), 7.36-7.63 (7H, m, ArH), 8.00-8.06 (1H, m, ArH).

Synthetic Example 2

Preparation of (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl-2(R)-2-butanol S,S-dioxide

(a) 0-(2-benzoyl-5-methoxyphenyl) dimethylthiocarbamate

Sodium hydride(8.8 g, Aldrich) was added slowly to a solution of 2-hydroxy-4-methoxybenzophenone(50.0 g, Aldrich) in 300 ml of dimethylformamide.

Hexamethylphosphoramide (43.0 g) was then added dropwise and stirred at room temperature for 2 hours. Dimethylthiocarbamoyl chloride(37.0 g, Aldrich) was added and stirred overnight at 50°C. The reaction mixture was poured into deionized water (300mL) and extracted with a petroleum ether/chloroform (1:4) mixture. The organic layer was washed with 10% sodium hydroxide, brine and concentrated to give the title product as a yellow solid(40.0g), mp 94-96°C. ¹H NMR was consistent with proposed structure.

(b) S-(2-Benzoyl-5-methoxyphenyl) dimethylthiocarbamate

The product(40.0g) from step(a) was suspended in phenyl ether(300mL) and heated to an internal temperature of 262°C for 30 minutes. After cooling to room temperature, the reaction mixture was chromatographed on silica using hexane, then hexanes/ethyl acetate(7:3) as eluants to afford the title product as a yellow-brown solid(30.0g), mp 96-98°C. ¹H NMR was consistent with proposed structure.

(c) 2-Mercapto-4-methoxybenzophenone

Potassium hydroxide pellets(20.0g) was slowly added to a solution of the product(28.0g) from step(b) dissolved in 800 ml methanol/tertbutylhydrofuran(1:1). After refluxing for 4 hours, the reaction was cooled to room temperature, methylene chloride was added and the solution was extracted with 5% hydrochloric acid. The organic layer was dried and concentrated. Chromatography on silica using hexanes/ethyl acetate(99:1) as the eluant

afforded the title product as a yellow solid (17.1g), mp 74-76°C. ¹H NMR consistent with proposed structure.

(d) (±)-2-But-2-enyl-3-ethyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiazepin-3-yl-2(R)-2-butanol S,S-dioxide

This compound was prepared following the procedure of Synthetic Example 1(b), using the product from step(c) (32.0g) and the product from Synthetic Example 1(f) (18.8g), but replacing ethereal HCl with p-toluenesulphonic acid (200 mg). Chromatography on silica using hexanes/EtOAc (9:1) as eluant gave the desired product as an orange oil (35.7g). ¹H NMR consistent with the proposed structure.

(e) (±)-2-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol

This compound was prepared following the procedure of Synthetic Example 1(i), using the product from step(d) (35.7g). Chromatography on silica using hexanes/EtOAc (65:35) as eluant afforded the title product as an orange oil (27.7g). ¹H NMR consistent with the proposed structure.

(f) (±)-2-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide

This compound was prepared following the procedure of Synthetic Example 1(i), using the product from step(e) (27.7g) to give solids which were recrystallized from acetone to give the desired product as a white solid (12.3g), mp 201-202°C.

Analysis: C 65.48; H 7.24; N 3.47; S 7.95
Found: C 65.51; H 7.29; N 3.38; S 8.01

¹H NMR (DMSO-d₆), δ: 0.79(3H, t, CH₃); 0.84(3H, t, CH₃); 1.22-1.30(2H, m, CH₂); 1.62-1.71(3H, m, CH₂); 2.21-2.26(1H, m, CH₂); 3.14(1H, d, NH); 3.45(2H, q, CH₂SO₂); 3.55-3.59(1H, m, CH); 3.78(3H, s, OCH₃); 4.52(1H, s, OH); 6.04(1H, d, CHPh); 6.42(1H, d, ArH); 7.02-7.05(1H, m, ArH); 7.29-7.43(6H, m, ArH)

Synthetic Example 3

Preparation of (±)-2-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide

(a) (±)-2-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide

This compound was isolated as a light yellow oil (4.7g) as a minor product of Synthetic Example 2(e). ¹H NMR consistent with the proposed structure.

(b) (±)-2-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide

This compound was prepared following the procedure of Synthetic Example 1(f), using the product from step(a) (3.0g) to give a white solid (0.70g), mp 119-122°C.

Analysis: C 65.48; H 7.24; N 3.47; S 7.95
Found: C 65.57; H 7.31; N 3.54; S 8.02

¹H NMR (DMSO-d₆), δ: 0.78-0.98(6H, m, CH₃); 1.10-1.26(2H, m, CH₂); 1.40-1.50(2H, m, CH₂); 1.73-1.84(1H, m, CH₂); 2.02-2.14(1H, m, CH₂); 2.50(1H, d, NH); 3.39(2H, q, CH₂SO₂); 3.42-3.51(1H, m, CH); 3.80(3H, s, OCH₃); 4.32(1H, d, OH); 5.87(1H, d, CHPh); 6.50(1H, d, ArH); 7.06(1H, dd, ArH); 7.28-7.48(6H, m, ArH)

Synthetic Example 4

Preparation of (±)-2-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide

(a) 2-Mercapto-5-methoxybenzophenone

This compound was prepared following the procedure of Synthetic Example 1(g), using 4-methoxybenzenethiol (20.0g, Aldrich). Chromatography on silica with hexanes/dichloromethane (1:1) as eluant afforded the title product as a yellow oil (2.9g). ¹H NMR consistent with the proposed structure.

(b) (±)-2-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide

Using ethyl iodide in place of crotyl bromide in step(c) of Synthetic Example 1, the title compound was prepared in an analogous fashion to give a colorless oil. ¹H NMR consistent with the proposed structure.

(b) (±)-2,2-Amino-2-ethylhexylthio-4'-benzylloxybenzophenone

The product from step(a)(15.0g) was dissolved in methanol(25 ml) and the product from Synthetic Example 6(b)(35.2g) in methanol(250 ml) was added. The mixture was stirred at room temperature for 17 hr and then concentrated in vacuo. The residue was chromatographed on silica with EtOAc then EtOAc/MeOH(1:1) as eluants to afford the title product as an orange oil(46.3g). ¹H NMR consistent with the proposed structure.

(c) (±)-2,2-Amino-2-ethylhexylsulfonyl-4'-benzylloxybenzophenone

This compound was prepared following the procedure of Synthetic Example 1(f), using the product from step(b)(46.3g). Chromatography on silica using EtOAc/MeOH(9:1) as the eluant gave the desired product as an orange oil(37.5g). ¹H NMR consistent with the proposed structure.

(d) (±)-3-Ethyl-3-butyl-5-(4-benzylloxyphenyl)-2,3-dihydrobenzothiazepine 1,1-dioxide

This compound was prepared following the procedure of Synthetic Example 1(b), using the product from step(c)(37.5g). Chromatography on silica using hexanes/EtOAc(7:3) as the eluant afforded the title product as an orange oil(24.8g). ¹H NMR consistent with the proposed structure.

(e) (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-benzylloxyphenyl)-1,4-benzothiazepine 1,1-dioxide

A 1M solution of diborane in THF(60.0 ml, Aldrich) was added to a solution of the product from step(d)(24.8g) in THF(150 ml). The mixture was stirred overnight at room temperature, then 6N HCl(100 ml) was added. The reaction mixture was concentrated in vacuo and the residue was partitioned between NaOH and EtOAc. The organic layer was separated, dried and concentrated. Chromatography on silica using hexanes/EtOAc(85:15) as eluant gave the desired product as a white solid(7.6g), mp 94-95°C. ¹H NMR consistent with the proposed structure.

(f) (±)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride

Palladium on carbon(10%, 2g, Aldrich) was added to a solution of formic acid(2.8g, Aldrich), sodium formate(1.0g, Fisher) and the product from step(e)(7.0g) in EtOH(250 ml). The reaction mixture was stirred at reflux for 5 hr, then stirred at room temperature for 17 hr. The reaction mixture was filtered, concentrated in vacuo and then dissolved in 1N NaOH. Next, 1N HCl was added till acid to litmus paper then solid NaHCO₃ was added to neutralize the solution. The mixture was extracted with diethyl ether, separated, dried and concentrated to give a light orange oil. Chromatography on silica using hexanes/EtOAc(7:3) as eluant afforded an oil which was treated with ethereal HCl to give the title product as a white solid(0.78g), mp 253-254°C.

Analysis: C 61.52; H 6.88; N 3.42; S 7.88

Found: C 61.52; H 6.93; N 3.48; S 7.90

¹H NMR(DMSO-d₆): δ: 0.80-0.91(6H, m, 2xCH₃); 1.25-2.02(8H, broad m, 4xCH₂); 2.50(1H, broad s, NH); 3.48(1H, broad s, CH₂SO₂); 4.10(1H, broad s, CH₂SO₂); 6.14(1H, broad s, CHPh); 6.96(4H, d, ArH); 7.36(2H, d, ArH); 7.64(2H, broad s, ArH); 8.05-8.08(1H, m, ArH); 10.0+11.3(1H, broad s, NH⁺)

Synthetic Example 8

Preparation of (±)-cis-3-ethyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride

(a) (±)-4-Ethyl-4-(hydroxymethyl)-2-oxazolidinone

Sodium methoxide(2.2g, Aldrich) was added to a solution of 2-amino-2-ethyl-1,3-propanediol(100.0g, Aldrich) and diethyl carbonate(169.0g, Aldrich). This solution was refluxed in a Dean Stark apparatus until no more EtOH was collected. The reaction mixture was cooled, added acetone(200 ml) and allowed to stand overnight at room temperature. The resulting suspension was filtered to give 81.0g of the desired product as a beige solid. ¹H NMR consistent with the proposed structure.

(b) (±)-4-Ethyl-4-[(tosyloxy)methyl]-2-oxazolidinone

Tosyl chloride (142.2g, Aldrich) was added to an ice-chilled solution of the product from step(e) (102.7 g) dissolved in pyridine (175 ml, Aldrich). The reaction mixture was stirred at ice bath temperature for six hours, then allowed to come to room temperature. The heterogeneous mixture was added to 1500 ml of a solution of brine and 1N HCl, stirred until solids appeared, filtered and washed with diethyl ether to give 194.6 g of a beige solid as the title product. ¹H NMR consistent with the proposed structure.

(c) *(±)-4-(((2-Benzoxylphenyl)thiomethyl)-4-ethyl-2-oxazolidinone*

2-Thiobenzophenone (125.3g, Synthetic Example 1(g)) in 150 ml of DMF was added slowly to sodium hydride (60%, 23.4g, Aldrich) in 175 ml of DMF. After complete addition, the product from step(b) (175.1g), in 200 ml of DMF, was added, in a steady stream, to the reaction mixture. The reaction was stirred at 60° C for 3 hr, cooled and added to 3L of brine to give solids. The reaction mixture was filtered and the solids were slurried in 250 ml of 95% EtOH and filtered to give the desired product as a beige solid (168.8g), mp 103-104°C. ¹H NMR consistent with the proposed structure.

(d) *(±)-2,3-Dihydro-3-ethyl-5-phenyl-1,4-benzothiazepine-3-methanol*

The product from step(c) (168.8g) was dissolved in 1200 ml EtOH/water(2:1) and 128.8g of KOH was added and refluxed for 24 hrs. The reaction mixture was cooled and concentrated in vacuo then ethyl acetate and deionized water were added. The organic layer was separated and concentrated in vacuo to give 155.2g of a red-orange oil. Chromatography on silica using hexanes/EtOAc(1:1) as eluant afforded the title product as a light orange oil (55.7g). ¹H NMR consistent with the proposed structure.

(e) *(±)-2,3-Ethyl-2,3-dihydro-5-phenyl-1,4-benzothiazepine-3-carbaldehyde*

Triethyl amine (56.7g, Aldrich) was added to a solution of the product from step(d) (55.7g) dissolved in 140 ml of DMSO. The reaction mixture was chilled to 8-10° C and sulfur trioxide pyridine complex (89.3g, Aldrich) in 200 ml of DMSO was added over a period of 16 minutes. The reaction mixture was stirred for 5 hr, allowing bath temperature to come to room temperature, then added to 3L of brine. This mixture was extracted with ethyl acetate which was separated, dried and concentrated to give 56.0g of a red oil. Hexanes (200ml) was added, allowed to stir until solids formed, and then filtered to give the desired product as a tan solid (43.1g), mp 98-100°C. ¹H NMR consistent with the proposed structure.

(f) *2-(3-Bromopropoxy)-2H-tetrahydropyran*

This compound was prepared by mixing 3-bromo-1-propanol (25.0g, Aldrich) and 3,4-dihydro-2H-pyran (22.7g, Aldrich) in dichloromethane (600 ml) and stirring for four hours at room temperature. Brine was added to the reaction mixture and the organic layer was separated, dried and concentrated to get a liquid. Chromatography on silica using hexanes/EtOAc(4:1) as eluant afforded the title product as a colorless liquid (37.9g). ¹H NMR consistent with the proposed structure.

(g) *3-Hydroxypropoxytriphenylphosphonium bromide*

The product from step(f) (47.8g) was added to a mixture of triphenyl phosphine (56.2g, Aldrich) and a few crystals of iodine in 1L of toluene. The reaction mixture was gently refluxed for a period of 62 hr, cooled and filtered to get a beige solid (55.2g), mp 227-228°C. ¹H NMR consistent with the proposed structure.

(h) *(±)-1-(2-Ethyl-2,3-dihydro-1,4-benzothiazepine-3-yl)-3-butanol*

A 2.5M solution of n-butyl lithium (20.0 ml, Aldrich) was added to an ice-chilled solution of the product from step(g) (9.6g) in THF (150 ml). After complete addition, the ice bath was removed and the product from step(e) (6.0g) in THF (20 ml) was added. The mixture was stirred at room temperature for 17 hr and then a saturated solution of NH₄Cl (20 ml) was added. The organic layer was separated, dried and concentrated in vacuo. Chromatography on silica using hexanes/EtOAc (85:15) as eluant gave the title product as an orange oil (4.6g). ¹H NMR consistent with the proposed structure.

(i) *(±)-1-(3-Ethyl-2,3-dihydro-1,4-benzothiazepine-3-yl)-3-butanol, 1,1-dioxide*

Alumina (12g, activity grade 1, type WB-2, basic, Sigma) was added in portions to Oxone (potassium peroxymonosulfate) (22.9g, Aldrich) and the product from step(h) (4.2g) in 100 ml CH₂Cl₂. The reaction mixture was stirred at gentle reflux for 3 hr then at room temperature for 17 hr. The mixture was filtered and the filtrate was washed with 5% NaHCO₃. The organic layer was separated, dried and concentrated to give an orange oil (3.4g). ¹H NMR consistent with the proposed structure.

(j) *(±)-Cis-3-Ethyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride*

The product from step(i)(3.4g) was dissolved in 60 ml of EtOAc and 1.7g of 10% Pd/C(Aldrich) was added, then placed on a Parr hydrogenator for 10 days. The reaction mixture was filtered and concentrated in vacuo to give an oil. Chromatography on silica using hexanes/EtOAc(3:2) as eluant gave a slightly yellow oil which was treated with ethereal HCl to give the title product as a white solid(0.50g), mp 193-194°C.

Analysis: Calcd. C 61.52; H 6.88; N 3.42; S 7.82

Found: C 61.50; H 6.86; N 3.43; S 7.88

¹H NMR of the free base(DMSO-d₆), δ: 0.80(3H, t, CH₃); 1.10-1.55(6H, m, 3xCH₂); 1.75-1.85(1H, m, CH₂); 1.96-2.07(1H, m, CH₂); 2.60(1H, d, NH); 3.20-3.35(2H, m, CH₂); 3.40(2H, q, CH₂SO₂); 4.27(1H, t, OH); 5.94(1H, d, CHPh); 6.42-6.50(1H, m, ArH); 7.30-7.43(7H, m, ArH); 7.93-7.99(1H, m, ArH)

Synthetic Example 9

Preparation of (+)-trans-3-butyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide

This compound was isolated from Synthetic Example 8(i) as an orange oil which upon stirring in EtOH/water afforded a white solid(0.070g), mp 136-139°C.

Analysis: C 67.53; H 7.29; N 3.75; S 8.59

Found: C 67.93; H 7.60; N 3.58; S 8.30

¹H NMR(DMSO-d₆), δ: 0.66(3H, t, CH₃); 1.20-1.44(6H, m, 3xCH₂); 1.70-1.78(1H, m, CH₂); 2.11-2.18(1H, m, CH₂); 2.63(1H, d, NH); 3.36-3.40(2H, m, CH₂); 3.39(2H, q, CH₂SO₂); 4.33(1H, t, OH); 5.94(1H, d, CHPh); 6.55-6.58(1H, m, ArH); 7.29-7.47(7H, m, ArH); 7.95-7.98(1H, m, ArH)

Synthetic Example 10

Preparation of (+)-trans-3-butyl-2,3,4,5-tetrahydro-7-hydroxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide

(a) Bis(4-isopropoxyphenyl)disulfide

A mixture of bis(4-hydroxyphenyl)disulfide (88.0g, Parish), potassium carbonate (194.0g), 2-bromopropane (297.6g) and anhydrous dimethylformamide (1500 ml) were stirred at room temperature for 2 days. Inorganics were filtered and the filtrate was concentrated. The residue was partitioned between ethyl acetate (600 ml) and brine (300 ml). The organic layer was separated, washed with brine, dried and concentrated to give the title product as a beige solid (112.4g), mp 62-64°C. ¹H NMR consistent with the proposed structure.

(b) 4-(isopropoxy)benzenethiol

Ethanol (225 ml) and the product from step (a) (33.8g) were mixed under N₂ and sodium borohydride (7.6g) was added in several portions. The mixture was refluxed for 2 hours, conc. HCl was added to bring the pH to 2 and the mixture concentrated in vacuo. The residue was partitioned between dichloromethane (200 ml) and water (200 ml). The organic layer was separated, washed with brine, dried and concentrated to give the title product as a yellow oil(30.5g). ¹H NMR consistent with the proposed structure.

(c) 2-Mercapto-5-(isopropoxy)benzophenone

This compound was prepared following the procedure of Synthetic Example 1(g), using the product from step (b) (39.6 g). Chromatography on silica with hexanes/dichloromethane (2:1) as eluant afforded the title product as an orange oil (24.0g). ¹H NMR consistent with the proposed structure.

(d) (+)-3-Butyl-2-ethyl-7-(isopropoxy)-5-phenyl-2,3-dihydrobenzothiazepine

This compound was prepared following the procedure of Synthetic Example 1(b), using the product from step (c) (24.0g). Chromatography on silica with hexanes/toluene (1:1) as eluant afforded the title product as a yellow oil (20.8 g). ¹H NMR consistent with the proposed structure.

(c) **(\pm)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-(isopropoxy)-5-phenyl-1,4-benzothiazepine**

This compound was prepared following the procedure of Synthetic Example 1(f), using the product from step (d) (20.8g). Gradient chromatography on silica with hexanes/toluene (1:1), toluene and ethyl acetate as the eluents afforded the title product as a yellow oil (8.2g). ¹H NMR consistent with the proposed structure.

(f) **(\pm)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-(isopropoxy)-5-phenyl-1,4-benzothiazepine 1,1-dioxide**

This compound was prepared following the procedure of Synthetic Example 1(f), using the product from step (e) (8.2g). Chromatography on silica with hexanes/ethyl acetate (6:1) as eluant afforded the title product as a white solid (1.9g). ¹H NMR consistent with the proposed structure.

(g) **(\pm)-Trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide**

The product from step(f) (1.4g) was dissolved in dichloromethane (108 ml) under N₂ and cooled to -10°C. A 1M solution of boron trichloride in dichloromethane (92 ml, Aldrich) was added dropwise. The reaction was stirred at -10°C for 30 minutes. Water (68 ml) was added dropwise and the mixture was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate (200 ml) and dichloromethane (200 ml) were added. The organic layer was separated, dried and concentrated. Chromatography on silica with hexanes/ethyl acetate (2:1) as eluant afforded the title product as an off-white solid (0.9g), mp 80-82°C.

Analysis: Calcd. C 67.53; H 7.35; N 3.69; S 8.44

Found: C 67.34; H 7.28; N 3.70; S 8.68

¹H NMR (DMSO-d₆): δ : 0.72-0.85(6H, m, CH₃), 1.07-1.23(4H, m, CH₂), 1.40-1.48(2H, m, CH₂), 1.60-1.82(1H, m, CH₂), 2.00-2.20(1H, m, CH₂), 2.58(1H, d, NH), 3.27(2H, q, CH₂SO₂), 5.92(1H, d, CHPh), 6.02(1H, d, ArH), 6.65(1H, dd, ArH), 7.41(3H, s, ArH), 7.80(1H, d, ArH), 10.27(1H, s, OH).

Synthetic Example 11

Preparation of (\pm)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-(2S)-2-butanol-S,S-dioxide

a) (3,3,3-Trifluoropropyl)triphenylphosphonium iodide

A solution of triphenylphosphine (Aldrich, 11.7g) and 3,3,3-trifluoropropyl iodide (Lancaster, 10g) was vigorously refluxed in xylenes (75ml) for 2 days. The solid which formed was filtered and washed with xylenes then air dried to yield a white solid (16.6g). ¹H NMR and elemental analysis are consistent with the proposed structure.

b) (\pm)-[2,3-Ethyl-2,3-dihydro-5-phenyl-3-(4,4,4-trifluoro-1-butyl)-1,4-benzothiazepine

The product from step(a) (16.5g) was slurried in tetrahydrofuran (THF) (250ml) then cooled with a dry-ice/acetone bath. n-Butyl lithium (Aldrich, 2.5M, 22.0ml) was added dropwise slowly. When the addition was complete, the bath was removed and the mixture allowed to warm to -30°. The reaction was cooled with a dry-ice/acetone bath and the aldehyde from Synthetic Example 8(c) (11.1g) in THF (50ml) was added by cannula. The solution was allowed to warm to room temperature overnight. The reaction was diluted with ethyl ether, filtered through Celite™, and evaporated to crude solids. Crystallization from petroleum ether/ethyl ether/hexanes yielded a crop (1.9g). The remaining material was chromatographed on silica gel with a suction column using 4% ethyl acetate/petroleum ether. The appropriate fractions were combined and evaporated to give a second crop of the desired product as a solid (8.47g combined). ¹H NMR and elemental analysis are consistent with the proposed structure.

c) (\pm)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-(2S)-2-butanol

The product from step(b) (8.3g) was dissolved in THF (60ml). Borane-THF (Aldrich, 1M/THF, 22ml) was added dropwise and the solution was stirred at room temperature overnight. Aqueous hydrochloric acid (HCl) (6N, 20ml) was added dropwise followed by evaporation of the solvent under reduced pressure. The yellow residue was treated with excess aqueous sodium hydroxide (NaOH) (45ml/1N) and extracted into ethyl acetate. The solvent was evaporated to an oil which was dissolved in THF

and then treated with aqueous NaOH (22mL/5N) and hydrogen peroxide (11mL/aqueous 30%). This mixture was stirred overnight at room temperature with vigorous stirring. The reaction was diluted with ethyl acetate and the organic layer separated, washed with a dilute solution of sodium bisulfite, and evaporated to a crude solid. This solid was chromatographed on silica gel with a suction column using 4:20% ethyl acetate/petroleum ether. The appropriate fractions were combined and evaporated to give the desired product as a solid (1.3g). Recovered starting material (3.7g) was treated with borane following the same procedure and chromatographed to give a second crop of the desired product as a solid (1.0g). ¹H NMR consistent with the proposed structure.

d) (±)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2-butanol-S,S-dioxide

The compound was prepared following the procedure from Synthetic Example 1(f), but using the product from step(c) (1.0g). The crude solids were crystallized from acetone/hexanes, filtered and dried to give the desired product, mp 164-168°C (0.4g).

Analysis: Calcd.: C 59.00; H 5.66; N 3.28; S 7.50;

Found: C 59.09; H 5.65; N 3.34; S 7.57

¹H NMR (DMSO-d₆): δ: 0.88 (3H, t, CH₃); 1.75 (3H, m); 2.10 (0.7H, s); 2.29 (3H, m); 3.21 (1H, d); 3.38 (1H, d); 3.80 (1H, d); 4.07 (1H, br m, CH(OH)); 5.03 (1H, s, OH); 6.15 (d, 1H); 6.54 (m, 1H); 7.43 (m, 7H, ArH); 7.98 (m, 1H).

Synthetic Example 12

Preparation of (±)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2-butanol-S,S-dioxide

a) (2)-3-Ethyl-2,3-dihydro-7-methoxy-5-phenyl-3-(4,4-trifluoro-1-butenyl)-1,4-benzothiazepine

The product was prepared following the procedures from Synthetic Example 8(a)-(c) and Synthetic Example 11(a)-(b) but using 2-(2-phenyl-1,3-dioxolan-2-yl)-4-methoxythiophenol(Riecke Metals). The crude solid was chromatographed on silica

gel with a suction column using 5% ethyl acetate/petroleum ether to give the desired product as a solid (14.0g). ¹H NMR consistent with the proposed structure.

b) 1-(3-Ethyl-7-methoxy-5-phenyl-2,3-dihydrobenzothiazepine)-4,4-trifluoro-2-butanol

The product from step(a) (14.0g) was dissolved into tetrahydrofuran (THF) (156mL). Borane-THF (Aldrich, 1M/THF, 39mL) was added dropwise to the warm solution. The solution was refluxed for 3 hours, cooled and carefully quenched with excess aqueous sodium hydroxide (35mL/5N). The solution was then treated with hydrogen peroxide (10mL/aqueous 30%), warmed to 60°C for 1 hour, and cooled. The organic layer was separated, washed with dilute aqueous sodium bisulfite and brine, dried over sodium sulfate, and evaporated to an oil (13.5g) which was primarily one spot by thin layer chromatography. This oil was used without further purification.

c) (±)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol

The product from step(b) (13.5g) was dissolved in THF (75mL) and borane-THF (Aldrich, 40mL/1M) was added dropwise. The reaction was refluxed for 1 hour, cooled, and ethereal hydrochloric acid (Aldrich, 40mL/1M) was added. The reaction was heated at reflux for 6 hours, cooled, boron trifluoride etherate was added and heated back to reflux. After cooling the reaction was poured into a large excess of aqueous sodium bicarbonate, extracted with ethyl acetate, washed with brine, dried over sodium sulfate, and evaporated to a crude oil. The oil was chromatographed on silica gel with a suction column using 0-15% ethyl acetate/petroleum ether as eluant to give the desired product as a solid (2.4g). ¹H NMR consistent with the proposed structure.

d) (±)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol-S,S-dioxide

The product was prepared following the procedure from Synthetic Example 1(f) but using the products from step(c) to give a crude solid which was crystallized from ethyl ether/hexanes to give a solid, mp 168-170°C (0.75g). ¹³C NMR consistent with the proposed structure.

Analysis: Calcd.: C 57.76; H 5.73; N 3.06; S 7.01;

Found: C 57.88; H 5.77; N 3.08; S 7.00

¹H NMR (DMSO-d₆, δ: 0.87 (3H, t, CH₃); 1.68 (2H, m, CH₂); 1.80 (1H, d); 2.30 (2H, m, CH₂); 2.41 (1H, dd); 3.11 (1H, d); 3.67 (3H, s, OCH₃); 3.71 (1H, d); 4.06 (1H, m); 5.00 (1H, d, OH); 5.95 (1H, d, ArH); 6.09 (1H, d, CHPh); 7.04 (1H, dd, ArH); 7.31-7.46 (5H, m, ArH); 7.93 (1H, d, ArH).

Each of the following compounds of formula (I) was prepared by a method analogous to one of the synthetic routes described above. In all cases ¹H NMR and elemental analysis were consistent with the proposed structure.

Synthetic Examples 13-57

- 13) (+)-*Trans*-2,3,4,5-Tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine-3-methanol 1,1-dioxide, mp 79-80°C;
- 14) (+)-*Cis*-2,3,4,5-Tetrahydro-3-methyl-5-phenyl-1,4-benzothiazepine-3-methanol 1,1-dioxide hydrochloride 0.25 hydrate mp 222-224°C;
- 15) (+)-*Trans*-4-(3-Butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-5-yl)phenol hydrochloride, mp 234-235°C(dec.);
- 16) (+)-*Trans*-5-(4-Benzoyloxyphenyl)-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine-3-methanol, mp 138-143°C;
- 17) (+)-*Trans*-3-Ethyl-2,3,4,5-tetrahydro-3-phenyl-1,4-benzothiazepine-3-methanol 1,1-dioxide, mp 134-137°C;
- 18) (+)-*Trans*-3-Ethyl-2,3,4,5-tetrahydro-3-(3-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide, mp 151-155°C;
- 19) (+)-*Cis*-3-Ethyl-2,3,4,5-tetrahydro-3-butyl-4-hydroxy-5-(3-pyridyl)-1,4-benzothiazepine 1,1-dioxide, mp 202-205°C;
- 20) (+)-*Cis*-4-(3-Butyl-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-5-yl)phenol hydrochloride, mp 236-237°C(dec.);
- 21) (+)-*Cis*-3-Butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 163-165°C;
- 22) (+)-*Cis*-3-Ethyl-2,3,4,5-tetrahydro-3-(3-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride, mp 206-209°C;
- 23) (+)-*Trans*-3-Ethyl-2,3,4,5-tetrahydro-3-(2(R)-2-hydroxybutyl)-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 197-198°C;

- 24) (+)-*Trans*-3-Ethyl-2,3,4,5-tetrahydro-3-(2(S)-2-hydroxybutyl)-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide, mp 178-179°C;
- 25) (+)-*Trans*-3-Ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine-3-methanol, mp 104-106°C;
- 26) (+)-*Cis*-5-(4-Benzoyloxyphenyl)-3-ethyl-2,3,4,5-tetrahydro-1,4-benzothiazepine-3-methanol, mp 123-128°C;
- 27) (+)-*Trans*-1-(3-Ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide, mp 130-132°C;
- 28) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(R)-2-butanol S,S-dioxide, mp 140-145°C;
- 29) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-5-phenyl)-1,4-benzothiazepin-3-yl)-4-fluoro-2-(R)-2-butanol S,S-dioxide 0.50 hydrate, mp 130-147°C;
- 30) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(S)-2-butanol S_oxide, mp 159-161°C;
- 31) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(S)-2-butanol S,S-dioxide, mp 168-170°C;
- 32) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(S)-2-butanol S,S-dioxide, mp 175-179°C;
- 33) (+)-*Trans*-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide, mp 156-157°C;
- 34) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- 35) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-3,3,4,4,4-pentafluoro-2-butanol S,S-dioxide;
- 36) (+)-*Trans*-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-3,3,4,4,4-pentafluoro-2-butanol S,S-dioxide;
- 37) (+)-*Trans*-3-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl)-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-7-yloxy)propanesulfonic acid 1,1-dioxide;
- 38) (+)-*Trans*-3-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl)-3-(4,4,4-trifluoro-2-

- hydroxybutyl)-1,4-benzothiazepin-8-yloxy)propanesulfonic acid 1,1-dioxide;
- 39) (+)-Trans-3-(3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl-1,4-benzothiazepin-7-yloxy)ethyltrimethylammonium iodide 1,1-dioxide;
- 40) (+)-Trans-3-(3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl-1,4-benzothiazepin-8-yloxy)ethyltrimethylammonium iodide 1,1-dioxide;
- 41) (+)-Trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-diethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4-trifluoro-2-butanol S,S-dioxide;
- 42) (+)-Trans-3-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-7-yloxy)ethyltrimethylammonium iodide 1,1-dioxide
- 43) (+)-Trans-3-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-8-yloxy)ethyltrimethylammonium iodide 1,1-dioxide;
- 44) (+)-Trans-3-(3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl-1,4-benzothiazepin-8-yloxy)propanesulfonic acid 1,1-dioxide;
- 45) (+)-Trans-3-(3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl-1,4-benzothiazepin-7-yloxy)propanesulfonic acid 1,1-dioxide;
- 46) (+)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-diethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
- 47) (+)-Trans-1-(3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- 48) (+)-Trans-1-(3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- 49) (+)-Trans-1-(3-Ethyl-2,3,4,5-tetrahydro-9-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- 50) (+)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-9-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
- 51) (+)-Trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- 52) (+)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-1-butanol S,S-dioxide;

- 53) (+)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-1-butanol S,S-dioxide;
- 54) (+)-Trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
- 55) (+)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-1-butanol S,S-dioxide;
- 56) (+)-Trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-1-butanol S,S-dioxide
- 57) (+)-Trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl-1,4-benzothiazepin-3-yl)-2-butanone S,S-dioxide

Pharmaceutical Composition Examples

In the following Examples, the active compound can be any compound of formula (I) and/or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The active compound is preferably one of the compounds of synthetic examples 1 to 63

(i) Tablet compositions

The following compositions A and B can be prepared by wet granulation of ingredients (a) to (c) and (a) to (d) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition A	mg/tablet	mg/tablet
(a) Active ingredient	250	250
(b) Lactose B.P.	210	26
(c) Sodium Starch Glycolate	20	12
(d) Povidone B.P.	15	9
(e) Magnesium Stearate	5	3
	500	300

Composition B

	mg/tablet	mg/tablet

53

(a) Active ingredient	250	250
(b) Lactose	150	150
(c) Avicel PH 101	60	26
(d) Sodium Starch Glycolate	20	12
(e) Povidone B.P.	15	9
(f) Magnesium Stearate	5	3
	500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions D and E can be prepared by direct compression of the admixed ingredients. The lactose used in composition E is of the direct compression type.

Composition D

	mg/tablet
Active ingredient	250
Magnesium Stearate	4
Pregelatinised Starch NF15	146
	400

Composition E

	mg/tablet
Active ingredient	250
Magnesium Stearate	5
Lactose	145
Avicel	100
	500

54

Composition F (Controlled release composition)

	mg/tablet
(a) Active ingredient	500
(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.C.	28
(e) Magnesium Stearate	7
	700

The composition can be prepared by wet granulation of ingredients (a) to (c) with a solution of povidone, followed by addition of the magnesium stearate and compression.

Composition G (Enteric-coated tablet)

Enteric-coated tablets of Composition C can be prepared by coating the tablets with 25mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

Composition H (Enteric-coated controlled release tablet)

Enteric-coated tablets of Composition F can be prepared by coating the tablets with 50mg/tablet of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

(ii) Capsule compositions

Composition A

Capsules can be prepared by admixing the ingredients of Composition D above and filling two-part hard gelatin capsules with the resulting mixture. Composition B (*infra*) can be prepared in a similar manner.

Composition B

	mg/capsule
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycolate	25
(d) Magnesium Stearate	2
	420

Composition C

	mg/capsule
(a) Active ingredient	250
(b) Macrogol 4000 BP	350
	600

Capsules can be prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling two-part hard gelatin capsules therewith.

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules can be prepared by dispersing the active ingredient in the lecithin and arachis oil and filling soft, elastic gelatin capsules with the dispersion.

Composition E (Controlled release capsule)

mg/capsule

(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Ethyl Cellulose	13
	513

The controlled release capsule formulation can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with a release controlling membrane (d) and filled into two-part, hard gelatin capsules.

Composition F (Enteric capsule)

	mg/capsule
(a) Active ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Cellulose Acetate Phthalate	50
(e) Diethyl Phthalate	5
	555

The enteric capsule composition can be prepared by extruding mixed ingredients (a) to (c) using an extruder, then spheronising and drying the extrudate. The dried pellets are coated with an enteric membrane (d) containing a plasticizer (e) and filled into two-part, hard gelatin capsules.

Composition G (Enteric-coated controlled release capsule)

Enteric capsules of Composition E can be prepared by coating the controlled-release pellets with 50mg/capsule of an enteric polymer such as cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, or anionic polymers of methacrylic acid and methacrylic acid methyl ester (Eudragit L). Except for Eudragit L, these polymers should also include 10% (by weight of the quantity of polymer used) of a plasticizer to prevent membrane cracking during application or on storage. Suitable plasticizers include diethyl phthalate, tributyl citrate and triacetin.

57

(iii) Intravenous injection composition

Active ingredient 0.200g
Sterile, pyrogen-free phosphate buffer (pH 9.0) to 10 ml

The active ingredient is dissolved in most of the phosphate buffer at 35-40°C, then made up to volume and filtered through a sterile micropore filter into sterile 10 ml glass vials (Type 1) which are sealed with sterile closures and oversealed.

(iv) Intramuscular injection composition

Active ingredient 0.20 g
Benzyl Alcohol 0.10 g
Glycofurl 75 1.45 g
Water for Injection q.s. to 3.00 ml

The active ingredient is dissolved in the glycofurl. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (Type 1).

(v) Syrup composition

Active ingredient 0.25g
Sorbitol Solution 1.50g
Glycerol 1.00g
Sodium Benzoate 0.005g
Flavour 0.0125ml
Purified Water q.s. to 5.0ml

The sodium benzoate is dissolved in a portion of the purified water and the sorbitol solution added. The active ingredient is added and dissolved. The resulting solution is mixed with the glycerol and then made up to the required volume with the purified water.

(vi) Suppository composition

mg/suppository

58

Active ingredient 250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel) 1770
2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200µm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension which is stirred to ensure a homogeneous mix. The entire suspension is then passed through a 250µm stainless steel screen and, with continuous stirring, allowed to cool to 40°C. At a temperature of 38-40°C, 2.02g aliquots of the mixture are filled into suitable plastic moulds and the suppositories allowed to cool to room temperature.

(vii) Pessary composition

mg/pessary

Active ingredient (63µm) 250
Anhydrous Dextrose 380
Potato Starch 363
Magnesium Stearate 7
1000

The above ingredients are mixed directly and pessaries prepared by compression of the resulting mixture.

(viii) Transdermal composition

Active ingredient 200mg
Alcohol USP 0.1ml
Hydroxyethyl cellulose

The active ingredient and alcohol USP are gelled with hydroxyethyl cellulose and packed in a transdermal device with a surface area of 10 cm².

Biological Assay

In vitro inhibition of bile acid uptake

Freshly prepared rat distal ileal brush border membrane vesicles (about 200mg vesicle protein) were incubated for 30 seconds at 24°C in an incubation mixture comprising 10mM ^3H taurocholate, 100mM NaCl (or KCl) and 80mM mannitol in 20mM Hepes Tris pH 7.4. Each test compound was dissolved in ethanol (or water) and then diluted with incubation mixture to an ethanol concentration of not more than 1% v/v. The incubation was terminated by rapid dilution and filtration and the filter washed with an ice-cold isotonic sodium-free buffer.

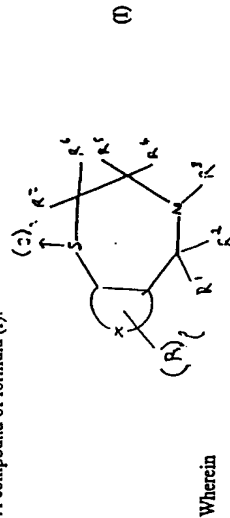
The uptake of ^3H taurocholate was measured by the radioactivity remaining on the filter and converted to pmoles/mg vesicle protein. The active, ie sodium-dependent, uptake was obtained by subtracting the passive uptake measured in 100mM KCl from the total uptake measured in 100mM NaCl. The active uptake for each test compound was compared with a control active uptake and the results expressed as % inhibition of bile acid uptake.

Data is given below for % inhibition of bile acid uptake at various concentrations of compounds of the invention.

Example	10 μM	3 μM	1 μM	0.3 μM
11	85	63	31	13
12	95	86	72	47
2	83	60	44	22
10	96	79	41	23
1	69	36		
8	70	51	31	19
9	27	16	15	
24	23			

CLAIMS

1. A compound of formula (I):



l is an integer of from 0 to 4;

n is an integer of from 0 to 2;

R is an atom or group selected from halogen, cyano, hydroxy, nitro, alkyl, alkoxy, aryl, heteroaryl, aryloxy, aryloxyalkoxy, aralkyl, alkaryl, $-\text{O}(\text{CH}_2)_p\text{SO}_2\text{R}^{11}$, $-\text{O}(\text{CH}_2)_p\text{NR}^{11}\text{R}^{12}$, $-\text{O}(\text{CH}_2)_p\text{N}^+\text{R}^{11}\text{R}^{12}\text{R}^{14}$, $-\text{COR}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CH}_2\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{11}$, $-\text{NHSO}_2\text{R}^{11}$, $-\text{SR}^{11}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $-\text{SO}_3\text{R}^{11}$ or R is a group $-\text{OCH}_2\text{O}-$ which forms a further ring attached to X wherein p is an integer of from 1 to 4, R^{11} R^{12} are independently selected from hydrogen, C_{1-6} alkyl and phenyl and R^{14} is hydrogen or C_{1-6} alkyl, wherein said alkyl, alkoxy, aryl, heteroaryl, aryloxy, aryloxyalkoxy, aralkyl and alkaryl groups are optionally substituted by one or more atoms or groups selected from halogen, hydroxy, nitro, nitrile, alkyl, alkoxy, $-\text{COR}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{SO}_3\text{R}^{11}$ wherein R^{11} is as hereinbefore defined and $-\text{NR}^{14}\text{R}^{15}$ wherein R^{14} is as hereinbefore defined and R^{15} is hydrogen or C_{1-6} alkyl

R^1 is hydrogen or C_{1-6} alkyl;

R^2 is an atom or group selected from hydrogen, C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{1-4} alkoxy, pyrrol, thienyl, pyridyl, 1,3-benzodioxolo, phenyl and naphthyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, $-\text{COR}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CH}_2\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NHCOR}^{11}$, $-\text{NHSO}_2\text{R}^{11}$, $-\text{SR}^{11}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_3\text{R}^{11}$ (wherein R^{11} and R^{12} are as hereinbefore defined), $-\text{OCH}_2\text{O}-$, $\text{N}^+\text{R}^{11}\text{R}^{12}\text{R}^{13}$

61

and $-O(CH_2)_n SO_2 R^{11}$ (wherein n , R^{11} and R^{12} are as hereinbefore defined and R^{13} is hydrogen or C_{1-6} alkyl);

R^3 is hydrogen, hydroxy C_{1-6} alkyl, alkoxy or $-O-C_{1-6}$ Acyl;

R^4 is a group independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl, and C_{2-6} alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, oxo, $-OR^{14}$, $-CO_2 R^{14}$, $-NR^{14} R^{15}$, $-SR^{14}$, $-S(O)C_{1-6}$ alkyl, $-SO_2 R^{14}$ and $-SO_3 R^{14}$ (wherein R^{14} and R^{15} are as hereinbefore defined);

R^5 is a group independently selected from C_{2-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl and C_{2-6} alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, oxo, $-OR^{14}$, $-CO_2 R^{14}$, $-NR^{14} R^{15}$, $-SR^{14}$, $-S(O)C_{1-6}$ alkyl, $-SO_2 R^{14}$ and $-SO_3 R^{14}$ (wherein R^{14} and R^{15} are as hereinbefore defined);

or R^4 and R^5 , together with the carbon atom to which they are attached, form a C_{3-7} spiro cycloalkyl group which is optionally substituted by one or more atoms or groups independently selected from halogen, $-OR^{14}$, $-CO_2 R^{14}$, $-SO_3 R^{14}$ and $-NR^{14} R^{15}$ (wherein R^{14} and R^{15} are as hereinbefore defined);

R^6 and R^7 are independently selected from hydrogen and C_{1-6} alkyl; and

X is an aromatic or non-aromatic monocyclic or bicyclic ring system having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the thiazepine ring) wherein optionally one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur.

with the proviso that at least one of R , R^2 , R^4 and R^5 is hydroxy or a group containing hydroxy;

and salts, solvates and physiologically functional derivatives thereof.

2. A compound as claimed in Claim 1 wherein:

62

l is 0, 1, or 2;

n is 1 or 2; and

R^1 , R^6 and R^7 are all hydrogen; and

R^3 is hydrogen or hydroxy

3. A compound as claimed in Claim 2 which is a trans isomer wherein:

(a) l is 0 or 1;

n is 2; and

R^4 and R^5 are groups independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl and C_{2-6} alkynyl, wherein said alkyl, alkenyl, or alkynyl group may be substituted by one or more hydroxy groups, or R^4 and R^5 , together with the carbon atom to which they are attached, form a C_{3-7} spiro cycloalkyl group which can be substituted by one or more hydroxy groups; or

(b) l is 0 or 1;

n is 2;

R^2 is a phenyl group which may be substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, $-COR^{11}$, $-CO_2 R^{11}$, $-CONR^{11} R^{12}$, $-CH_2 OR^{11}$, $-NR^{11} R^{12}$, $-NHCOR^{11}$, $-NHSO_2 R^{11}$, $-SR^{11}$, $-SO_2 R^{11}$, $-SO_3 R^{11}$ (wherein R^{11} and R^{12} are independently selected from hydrogen, C_{1-6} alkyl and phenyl), $-O(CH_2)_n NR^{11} R^{12}$, $-O(CH_2)_n NR^{11} R^{12} R^{13}$ and $-O(CH_2)_n SO_3 R^{11}$ (wherein n is an integer of from 1 to 4, R^{11} and R^{12} are as hereinbefore defined and R^{13} is hydrogen or C_{1-6} alkyl);

R^4 and R^5 are groups independently selected from C_{1-6} alkyl (including cycloalkyl and cycloalkylalkyl), C_{2-6} alkenyl and C_{2-6} alkynyl, wherein said alkyl, alkenyl, or alkynyl group may be substituted by one or more hydroxy groups, or R^4 and R^5 ,

together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which can be substituted by one or more hydroxy groups; or

(c) i is 0 or 1;

n is 2;

R² is a phenyl group which may be substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzoyloxy, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₃R¹¹ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), -O(CH₂)_pNR¹¹R¹², -O(CH₂)_pNR¹¹R¹²R¹³ and -O(CH₂)_pSO₃R¹¹ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R⁴ and R⁵ are groups independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups can be substituted by one or more hydroxy groups; and

X is a fused phenyl, naphthyl, pyrrol, thienyl, or pyridyl group;

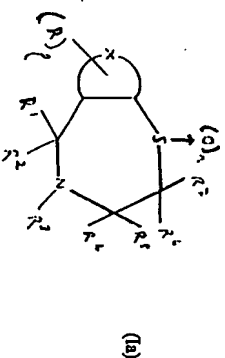
4. A compound as claimed in Claim 1 which is:

- (+)-trans-3-ethyl-2,3,4,5-tetrahydro-3-((2R)-2-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-3-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide 0.5 hydrate;

- (+)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide hydrochloride;
- (+)-cis-3-ethyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide hydrochloride;
- (+)-trans-3-ethyl-2,3,4,5-tetrahydro-3-(4-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-3-butyl-3-ethyl-2,3,4,5-tetrahydro-7-hydroxy-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-(2S)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-(2S)-2-butanol S,S-dioxide;
- (+)-trans-3-Ethyl-2,3,4,5-tetrahydro-3-(3-hydroxybutyl)-5-phenyl-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-3-Ethyl-2,3,4,5-tetrahydro-3-(2R)-2-hydroxybutyl)-5-(4-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide;
- (+)-trans-1-(3-Ethyl-5-(4-fluorophenyl)-2,3,4,5-tetrahydro-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(S)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2(S)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-2(R)-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-3,3,4,4-pentafluoro-2-butanol S,S-dioxide;
- (+)-trans-3-((3-ethyl-2,3,4,5-tetrahydro-5-phenyl-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-8-yloxy)propanesulfonic acid 1,1-dioxide;
- (+)-trans-3-((3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl-1,4-benzothiazepin-8-yloxy)ethyltrimethylammonium iodide 1,1-dioxide;
- (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
- (+)-trans-3-((3-ethyl-2,3,4,5-tetrahydro-5-phenyl-3-(4,4,4-trifluoro-2-hydroxybutyl)-1,4-benzothiazepin-8-yloxy)ethyltrimethylammonium iodide 1,1-dioxide;

- (+)-trans-3-(3-ethyl-2,3,4,5-tetrahydro-3-(2-hydroxybutyl)-5-phenyl)-1,4-benzothiazepin-8-yl)oxy)propanesulfonic acid 1,1-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dithoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
 (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dimethoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-1-butanol S,S-dioxide;
 (+)-trans-1-(3-Ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2-butanol S,S-dioxide;
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-8-methoxy-5-phenyl)-1,4-benzothiazepin-3-yl)-4,4,4-trifluoro-1-butanol S,S-dioxide; or
 (+)-trans-1-(3-ethyl-2,3,4,5-tetrahydro-7,8-dihydroxy-5-phenyl)-1,4-benzothiazepin-3-yl)-2-butanone S,S-dioxide

5. A compound as claimed in claim 1 of the formula (1a)



wherein
 1 is an integer of from 0 to 4;

n is an integer of from 0 to 2;

R is an atom or group selected from halogen, cyano, hydroxy, nitro, alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, aralkyl, alkaryl, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹ and -SO₃R¹¹ wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl, wherein said alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, alkaryl and alkaryl groups are optionally substituted by one or more atoms or groups selected from halogen, hydroxy, nitro, alkyl, alkoxy, -COR¹¹, -CO₂R¹¹, -

SO₂R¹¹ wherein R¹¹ is as hereinbefore defined and -NR¹⁴R¹⁵ wherein R¹⁴ and R¹⁵ are as hereinbefore defined;

R¹ is hydrogen or C₁₋₆ alkyl;

R² is an atom or group selected from hydrogen, C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₁₋₄ alkoxy, pyrrol, thienyl, pyridyl, 1,3-benzodioxolo, phenyl and naphthyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxyl, benzoyloxy, -COR¹¹, -CO₂R¹¹, -CONR¹¹R¹², -CH₂OR¹¹, -NR¹¹R¹², -NHCOR¹¹, -NHSO₂R¹¹, -SR¹¹, -SO₂R¹¹, -SO₃R¹¹ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), -O(CH₂)_pNR¹¹R¹², -O(CH₂)_pNR¹¹R¹²R¹³ and -O(CH₂)_pSO₃R¹¹ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R³ is selected from hydrogen, hydroxy and C₁₋₆ alkyl;

R⁴ is a group independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, -OR¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁵ and -SO₃R¹⁴ (wherein R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁₋₆ alkyl);

R⁵ is a group independently selected from C₂₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, -OR¹⁴, -CO₂R¹⁴, -NR¹⁴R¹⁵ and -SO₃R¹⁴ (wherein R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁₋₆ alkyl);

or R⁴ and R⁵, together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which is optionally substituted by one or more atoms or groups independently selected from halogen, -OR¹⁴, -CO₂R¹⁴, -SO₃R¹⁴ and -NR¹⁴R¹⁵ (where R¹⁴ and R¹⁵ are as hereinbefore defined);

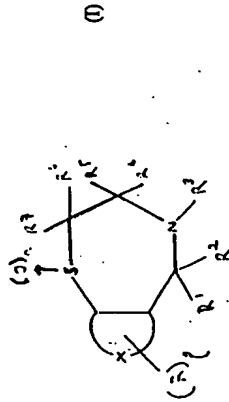
R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆ alkyl; and

X is an aromatic or non-aromatic monocyclic or bicyclic ring system

having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the thiazepine ring) wherein optionally one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur, with the proviso that at least one of R, R², R⁴ and R⁵ is hydroxy or a group containing hydroxy;

and salts, solvates and physiologically functional derivatives thereof.

6. A compound of formula (I):



wherein

1 is an integer of from 0 to 4;

n is an integer of from 0 to 2;

R is an atom or group selected from halogen, cyano, hydroxy, nitro, alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, alkyl, alkaryl, $-\text{O}(\text{CH}_2)_p\text{SO}_2\text{R}^{11}$, $-\text{O}(\text{CH}_2)_p\text{NR}^{11}\text{R}^{12}$, $-\text{O}(\text{CH}_2)_p\text{N}^+\text{R}^{11}\text{R}^{12}\text{R}^{14}$, $-\text{COR}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CH}_2\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NHCO}_2\text{R}^{11}$, $-\text{NHCO}_2\text{R}^{11}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $-\text{SO}_3\text{R}^{11}$ or R is a group $-\text{OCH}_2\text{O}-$ which forms a further ring attached to X wherein p is an integer of from 1 to 4, R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl and R¹⁴ is hydrogen or C₁₋₆ alkyl, wherein said alkyl, alkoxy, aryl, heteroaryl, aryloxy, arylalkoxy, alkaryl and alkaryl groups are optionally substituted by one or more atoms or groups independently selected from halogen, hydroxy, nitro, nitrile, alkyl, alkoxy, $-\text{COR}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{SO}_3\text{R}^{11}$ wherein R¹¹ is as hereinbefore defined and $-\text{NR}^{14}\text{R}^{15}$ wherein R¹⁴ is as hereinbefore defined and R¹⁵ is hydrogen or C₁₋₆ alkyl;

R¹ is hydrogen or C₁₋₆ alkyl;

R² is an atom or group selected from hydrogen, C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₁₋₄ alkoxy, pyrryl, thienyl, pyridyl, 1,3-benzodioxolo, phenyl and naphthyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, cyano, hydroxy, nitro, carboxyl, phenyl, phenoxy, benzyloxy, $-\text{COR}^{11}$, $-\text{CO}_2\text{R}^{11}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CH}_2\text{OR}^{11}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NHCO}_2\text{R}^{11}$, $-\text{NHCO}_2\text{R}^{11}$, $-\text{SR}^{11}$, $-\text{SO}_2\text{R}^{11}$, $-\text{SO}_3\text{R}^{11}$ (wherein R¹¹ and R¹² are independently selected from hydrogen, C₁₋₆ alkyl and phenyl), $-\text{O}(\text{CH}_2)_p\text{NR}^{11}\text{R}^{12}$, $-\text{O}(\text{CH}_2)_p\text{N}^+\text{R}^{11}\text{R}^{12}\text{R}^{13}$ and $-\text{O}(\text{CH}_2)_p\text{SO}_3\text{R}^{11}$ (wherein p is an integer of from 1 to 4, R¹¹ and R¹² are as hereinbefore defined and R¹³ is hydrogen or C₁₋₆ alkyl);

R³ is hydrogen, hydroxy C₁₋₆ alkyl, alkoxy or $-\text{O}-\text{C}_{1-6}\text{Acyl}$;

R⁴ is a group independently selected from C₁₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, oxo, $-\text{OR}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{NR}^{14}\text{R}^{15}$, $-\text{SR}^{14}$, $-\text{S}(\text{O})\text{C}_{1-6}\text{alkyl}$, $-\text{SO}_2\text{R}^{14}$ and $-\text{SO}_3\text{R}^{14}$ (wherein R¹⁴ and R¹⁵ are as hereinbefore defined);

R⁵ is a group independently selected from C₂₋₆ alkyl (including cycloalkyl and cycloalkylalkyl), C₂₋₆ alkenyl and C₂₋₆ alkynyl, which groups are optionally substituted by one or more atoms or groups independently selected from halogen, oxo, $-\text{OR}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{NR}^{14}\text{R}^{15}$, $-\text{SR}^{14}$, $-\text{S}(\text{O})\text{C}_{1-6}\text{alkyl}$, $-\text{SO}_2\text{R}^{14}$ and $-\text{SO}_3\text{R}^{14}$ (wherein R¹⁴ and R¹⁵ are as hereinbefore defined);

or R⁴ and R⁵, together with the carbon atom to which they are attached, form a C₃₋₇ spiro cycloalkyl group which is optionally substituted by one or more atoms or groups independently selected from halogen, $-\text{OR}^{14}$, $-\text{CO}_2\text{R}^{14}$, $-\text{SO}_3\text{R}^{14}$ and $-\text{NR}^{14}\text{R}^{15}$ (where R¹⁴ and R¹⁵ are as hereinbefore defined);

R⁶ and R⁷ are independently selected from hydrogen and C₁₋₆ alkyl; and

X is an aromatic or non-aromatic monocyclic or bicyclic ring system

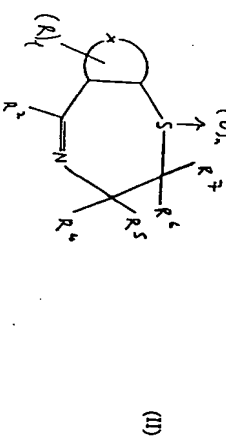
having from 5 to 10 carbon atoms (including the two carbon atoms forming part of the thiazepine ring) wherein optionally one or more of the carbon atoms is/are replaced by heteroatom(s) independently selected from nitrogen, oxygen and sulphur.

with the proviso that at least one of R , R^2 , R^4 and R^5 is hydroxy or a group containing hydroxy;

and salts, solvates and physiologically functional derivatives thereof, for use in the prophylaxis or treatment of clinical conditions for which a bile acid uptake inhibitor is indicated.

7. A compound as claimed in claim 6 for use in the prophylaxis or treatment of clinical conditions for which a bile acid uptake inhibitor is indicated.
8. A compound as claimed in Claim 7 for use in the prophylaxis or treatment of atherosclerosis.
9. A pharmaceutical formulation comprising a compound of formula (I) as defined in Claim 1, or of formula (Ia) as defined in claim 5 together with one or more pharmaceutically acceptable carriers and, optionally, one or more other physiologically active agents.
10. A pharmaceutical formulation as claimed in Claim 9 wherein the compound of formula (I) or (Ia) is as defined in any one of Claims 2 to 4.
11. The use of a compound as claimed in any one of Claims 1 to 5 in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a bile acid uptake inhibitor is indicated.
12. The use as claimed in Claim 11 wherein the medicament is for the prophylaxis or treatment of atherosclerosis.
13. A process for the preparation of a compound as claimed in Claim 1 which comprises at least the step of:

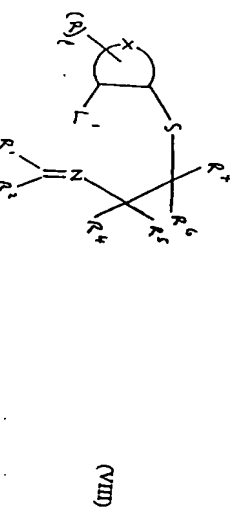
- (a) Wherein $n=0$ and R^1 and R^3 are hydrogen, reducing the imine bond of a compound of formula (II):



wherein $1, R, R^2, R^4$ to R^7 and X are as hereinbefore defined; or

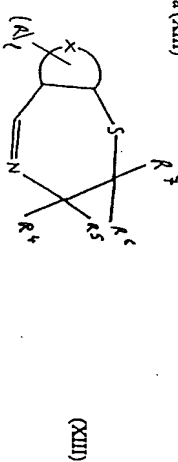
- (b) wherein $n=0$ and R^1 is not hydrogen, by alkylation of the corresponding compound of formula (II); or

- (c) wherein $n=0$ and R^3 is hydrogen, by cyclising a compound of formula (VIII):



wherein $1, R, R^2, R^4$ to R^7 and X are as hereinbefore defined and L^1 is halogen, by treatment with a strong base; or

- (d) wherein $n=0$ and R^1 and R^3 are both hydrogen, alkylating a compound of formula (XIII)

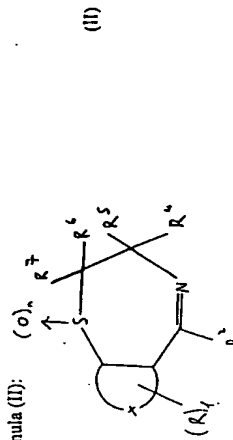


wherein $1, R, R^2, R^4$ to R^7 and X are as hereinbefore defined; or

- (e) by reaction of a compound of formula (I) wherein R^4 is C_{2-6} alkenyl with gaseous hydrogen halide to give the corresponding compound of formula (II) wherein R^4 is halogen substituted C_{2-6} alkyl, optionally followed by a hydrolysis step using H_2O_2 to give the corresponding compound of formula (I) wherein R^4 is hydroxy substituted C_{2-6} alkyl; or
- (f) by reduction and hydroxylation of a compound of formula (II) wherein R^4 is C_{2-6} alkenyl; or
- (g) by hydrogenation of a compound of formula (II) wherein R^4 is hydroxy substituted C_{2-6} alkenyl; or
- (h) by debenzoylation of a compound of formula (I) wherein R^2 is benzoyloxyphenyl; or
- (i) wherein $n=0$ and R^3 is not hydrogen, by N-alkylation of the corresponding compound of formula (II) with an alkyl halide, followed by reduction to a compound of formula (I), or
- (j) wherein n is 1 or 2 oxidation of the corresponding compound of formula (I) wherein n is 0; or
- (k) wherein n is 1 or 2, oxidation of the corresponding compound of formula (II) wherein n is 0 prior to cyclisation and reduction to the compound of formula (I).
14. A method of inhibiting the absorption of bile acids from the intestine of a mammal, such as a human, which comprises administering an effective bile acid absorption inhibiting amount of a compound of formula (I) as defined in claim 1, or of formula (Ia) as defined in claim 5, or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal.
15. A method of reducing the blood plasma or serum concentrations of LDL and VLDL cholesterol in a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I), as defined in claim 1, or of formula (Ia) as defined in claim 5, or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal.

16. A method of reducing the concentrations of cholesterol and cholesterol ester in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol and cholesterol ester reducing amount of a compound of formula (I), as defined in claim 1, or of formula (Ia) as defined in claim 5, or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal.
17. A method of increasing the faecal excretion of bile acids in a mammal, such as a human, which comprises administering an effective bile acid faecal excretion increasing amount of a compound of formula (I), as defined in claim 1, or of formula (Ia) as defined in claim 5, or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal.
18. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a bile acid uptake inhibitor is indicated, for example a hyperlipidaemic condition, such as atherosclerosis, which comprises administering a therapeutically effective amount of a compound of formula (I), as defined in claim 1, or of formula (Ia) as defined in claim 5, or of a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to the mammal.
19. A method of reducing the incidence of coronary heart disease-related events in a mammal, such as a human, which comprises administering an effective coronary heart disease-related events reducing amount of a compound of formula (I), as defined in claim 1, or of formula (Ia) as defined in claim 5, or of a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.
20. A method of reducing the concentration of cholesterol in the blood plasma or serum of a mammal, such as a human, which comprises administering an effective cholesterol reducing amount of a compound of formula (I), as defined in claim 1, or of formula (Ia) as defined in claim 5.

21. Intermediates of formula (II):



INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/00314

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 285/36, C07D 513/04, C07D 281/70, A61K 31/55
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search (name of data base and, where practicable, search terms used)

CA. MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	NO, A1, 9316055 (THE WELLCOME FOUNDATION LIMITED ET AL.), 19 August 1993 (19.08.93)	1-13, 21
X	US, A, 3362962 (EARL REEDER ET AL.), 9 January 1968 (09.01.68), see the claims; column 1, line 10 - line 12, line 45 - line 65; column 2, line 18 - line 43	1-10, 13, 21
X	NO, A1, 9221668 (THE BOOTS COMPANY PLC ET AL.), 10 December 1992 (10.12.92), see the claims	1-10

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

- * Special categories of cited documents:
- *X* document defining the general state of the art which is not considered to be of particular relevance
 - *Y* document published on or after the international filing date of the invention but published on or before the date of publication of the invention
 - *U* document which may show doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - *O* document referring to an oral disclosure, use, exhibition or other means
 - *P* document published prior to the international filing date but later than the priority date claimed
 - *G* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

31.05.94

27 April 1994

Name and mailing address of the ISA/
European Patent Office, P.O. Box 1818
NL-2130 HV Rijswijk
Tel. (+31-70) 485200, Telex 31 431 epo nl,
Fax (+31-70) 4852010

Authorized officer

GERD STRANDELL

Form PCT/ISA/210 (second sheet) (July 1993)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/00314

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB, A, 1181571 (E.R. SQUIBB & SONS INC.), 18 February 1970 (18.02.70), see the claims; page 1, line 15 - page 2, line 46 -----	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1993)

SA 478

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/02/94

International application No.
PCT/GB 94/00314

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9316055	19/08/93	AU-A- 3508293	03/09/93
US-A- 3362962	09/01/68	BE-A- 658798	26/07/65
		CH-A- 494207	31/07/70
		DE-A- 1545932	08/01/70
		FR-A- 4916	00/00/00
		FR-A- 1422569	00/00/00
		GB-A- 1091182	00/00/00
		NL-A- 6500817	26/07/65
		US-A- 3503985	31/03/70
		US-A- 3523974	11/08/70
		US-A- 3530139	22/09/70
		US-A- 3631089	28/12/71
WO-A1- 9221668	10/12/92	AU-A- 1880792	08/01/93
GB-A- 1181571	18/02/70	BE-A- 695313	11/09/67
		CH-A- 482706	15/12/69
		DE-A- 1695698	29/04/71
		FR-A- 1602881	08/02/71
		NL-A- 6703347	11/09/67
		US-A- 3794639	26/02/74

THIS PAGE BLANK (uspto)